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CONTRACTING ORGANIZATION: Ohio State University
Columbus, Ohio 43210-1063

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Patricia C. Modrow 8/4/02

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13. ABSTRACT *(Maximum 200 words)*

While there is clear evidence that psychological/behavioral interventions with cancer patients provide adjustment and coping benefits (Mark & Meyer, 1995) as well as positive immune and survival benefits (Fawzy et al., 1993; Speigel et al., 1989), the mechanisms for the benefits of such groups are not clearly understood. We propose that one of the mechanisms for the success of intervention groups may be through the provision of social support. Thus, by receiving needed support, patients may be "buffered" or protected from the more negative effects of the cancer stressor (e.g., depressive symptoms, Spiker, Trijsburg, & Duivenvoorden, 1997; and immune down-regulation, Andersen et al., 1998). Therefore, we are studying the impact of a psychological/behavioral intervention with breast cancer patients, using treatment (intervention) and control (no intervention) arms, on social support and endocrine responses.

Based on our proposed hypotheses we find at 4-month follow-up: (1) The intervention participants do not have significantly higher levels of social support than the assessment only subjects. (2) The intervention participants do have significantly fewer depressive symptoms and lower levels of cortisol than the assessment only subjects (Andersen et al., under review). Furthermore, psychological stress (i.e., perceived stress and life events), across groups, is associated with depressive symptoms (Golden-Kreutz et al., under review). (3) Participation in the intervention buffers women against the stressful effects (i.e., increased cortisol) of multiple group commitments (e.g., social, organizational, etc.).

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Breast Cancer, psychological/behavioral intervention, social support, endocrine function

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____ In the conduct of research utilizing recombinant DNA, the investigator(s) adhered to the NIH Guidelines for Research Involving Recombinant DNA Molecules.

____ In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.

DM Holden-Kreitz 8/23/99

PI - Signature Date

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Introduction

While there is clear evidence that psychological/behavioral interventions with cancer patients provide adjustment and coping benefits (Mark & Meyer, 1995) as well as positive immune and survival benefits (Fawzy et al., 1993; Speigel et al., 1989), the mechanisms for the benefits of such groups are not clearly understood. We proposed that one of the mechanisms for the success of intervention groups may be through the provision of social support. Thus, by receiving needed support, patients may be "buffered" or protected from the more negative effects of the cancer stressor (e.g., depressive symptoms, Spiker, Trijsburg, & Duivenvoorden, 1997; and immune down-regulation, Andersen et al., 1998). We proposed studying the impact of a psychological/behavioral intervention with breast cancer patients, using treatment (intervention) and control (no intervention) arms, on social support and endocrine responses. We also were interested in endocrine functioning as a biological marker of stress severity (Uchino, Cacioppo, & Kiecolt-Glaser, 1996) in breast cancer patients. Data from this study is being used to determine: (1) if an intervention is associated with significantly higher levels of social support among the intervention subjects, (2) if an intervention is associated with significantly lower endocrine stress responses among intervention subjects, and (3) test the stress buffering hypothesis of social support, that is test for an interaction between study arm (intervention vs. no intervention) and initial level of social support (high vs. low) across time (initial vs. post-treatment) on endocrine function (e.g., cortisol).

Body

A. Description of Training and Research Accomplishments to Date

The army funding, beginning in August 1997 (DAMD17-97-1-7062), has enabled the principal investigator to accomplish both research and professional goals, per the statement of work, as discussed below: Task 1 and Task 2 (Endocrine Panel Selection and Management), Task 3 (Management of Data), Task 4 (Professional Development), and Task 5 (Intervention Therapist).

Task 1 and Task 2: Endocrine Panel Selection and Management. Have meet regularly with Drs. Andersen and Malarkey over the past 2 years regarding endocrine data (collection, management, and analysis). These meetings have also included laboratory personnel as needed (e.g., proper collection of salivary CORT). The final endocrine panel of the larger study includes CORT, PRL, GH (results from frozen plasma), EPI, NEPI, and ACTH (results from fresh plasma), and we are also collecting salivary CORT. We have not experienced any significant problems with "unusual" values within or across assays.

We currently have completed CORT (plasma), PRL, and GH data on 112, 99, 92, and 90 women at the initial assessment time point, and 4, 8, and 12-month follow-ups, respectively. Because salivary CORT, EPI, NEPI, and ACTH were not collected until later in the larger project and because much of the endocrine data is analyzed in batches to reduce interassay variability, we have only 30 women with data, a number insufficient for running repeated measures analyses. However, over the next 3 months we expect to have additional data on approximately 50 women and will conduct analyses at that time. Additionally, we expect to have a similar increase in our data on CORT, GH, and PRL. Thus, having a no-cost extension year will allow us the time to not only add data points but to have the capability of running some of the endocrine analyses as proposed.

Task 3: Management of Data. We have continued to maintain checks on the collection, accuracy, and management of the social support data gathered through the larger study using regularly scheduled contacts (weekly staff meeting with research personnel). Again, we have not encountered any significant problems in data collection or management. For the present study, recruitment and accrual issues are not specific problems as the subjects are already participating in the larger study.

To date, in the larger study, we have collected initial data on 199 subjects (goal of 235) at the initial time point and 160, 155 and 134 at the 4, 8, and 12 month assessments, respectively. Note, eligible women are newly diagnosed and/or recently treated women with Stage II or III breast cancer. Following accrual, women are randomized between intervention and assessment only arms and followed every 4 months during the year, a total of 4 assessment time points. The study dropout rate at 12 months of participation is extremely low at 6.5%. Thus, we have been very successful in keeping subjects in the study. Also, we have conducted analyses, as proposed, examining for potential bias between the intervention and assessment only arms at the initial assessment. We have found no significant differences between arms on sociodemographic (age, race, family income, education) or randomization criteria (tumor size, number of positive lymph nodes, estrogen receptor status, menopausal status, and presence/absence of partner/spouse). Therefore, we have data to support that our results are not confounded by pre-intervention vs. assessment only group differences.

Task 4: Professional Development. During the past 2 years, I received behavioral medicine training in the following areas:

(1) Extensive reading of the PNI literature with additional focus on endocrine research (under the direction of Drs. Malarkey and Andersen). This reading has been important in the development of studies and preparation of manuscripts.

(2) Extensive reading of the stress and cancer literature including the research on PTSD in cancer populations. Based on these readings, I am working with Dr. Andersen and her graduate students in the preparation of several publications (Golden-Kreutz et al., under review; Golden-Kreutz et al., in progress) in relation to the stress experience of women with breast cancer as well as supervising the research work of psychology graduate students (formulating research ideas, planning research projects, writing abstracts for conference presentations).

(3) Attended meetings of the Health Psychology Graduate Colloquium Series in the Department of Psychology. This Health Psychology Series emphasizes current research and professional issues in the field and is regularly attended by faculty, postdocs, and graduate students in psychology. Additionally, I presented a talk (November, 1997) titled "The role of health psychologists in the assessment and management of organ recipients: A case study of liver transplantation" based on my clinical experience with medical patients. Also, attended meetings of the PNI Journal Club for PNI faculty (e.g., Andersen, Malarkey, Kiecolt-Glaser, Glaser), graduate students, and medical residents across university departments (including medicine,

immunology, endocrinology, psychology, oral biology). I also presented to the Journal Club (February, 1998) published data from the larger study, a publication (Andersen et al., 1998) in which I was involved.

(4) Obtained training in CEFA, Comprehensive Exploratory Factor Analysis, a computer program for conducting factor analyses created by Dr. Michael Browne. This program was used to analyze stress measurement data from the larger project and is currently being written for publication (Golden-Kreutz et al., in progress) with Dr. Browne as one of the coauthors.

(5) For further behavior medicine training I also attended the following conferences/invited presentations: Barbara Rimer, DR.P.H, invited address ("Cancer Risk and the Impact of Genetic Testing") at the James Cancer Hospital and Research Institute, Columbus, Ohio (February, 1998), and Psychosocial Interventions and Cancer Conference at the University of Pittsburgh Cancer Institute, Pittsburgh, PA (October, 1998). I was also active in additional professional development activities (e.g., improving writing skills, expanding collegial contacts, and presenting research findings at national/international meetings. Due to space limitations, references of presentations, chapters, and papers I was involved in writing or am currently in the process of writing are listed in the Appendix B.

Task 5: Intervention Therapist. I continue to be the lead co-therapist for the larger project. To date, I have lead 10 intervention groups (9 through the entire one year intervention). As a licensed psychologist I operate independently in leading the group and collecting process data. As necessary I confer with Dr. Andersen regarding group processes and/or data issues. I have also spent the last 2 years training advanced level clinical psychology graduate students in conducting the group intervention. In the training of students, we have weekly supervision meetings regarding group process, therapeutic techniques, and teaching cognitive/behavioral stress management skills to women with breast cancer. As the group therapist, I have gained skills as a psychotherapist, group therapist, and supervisor/teacher.

B. Analysis of Hypotheses to Date

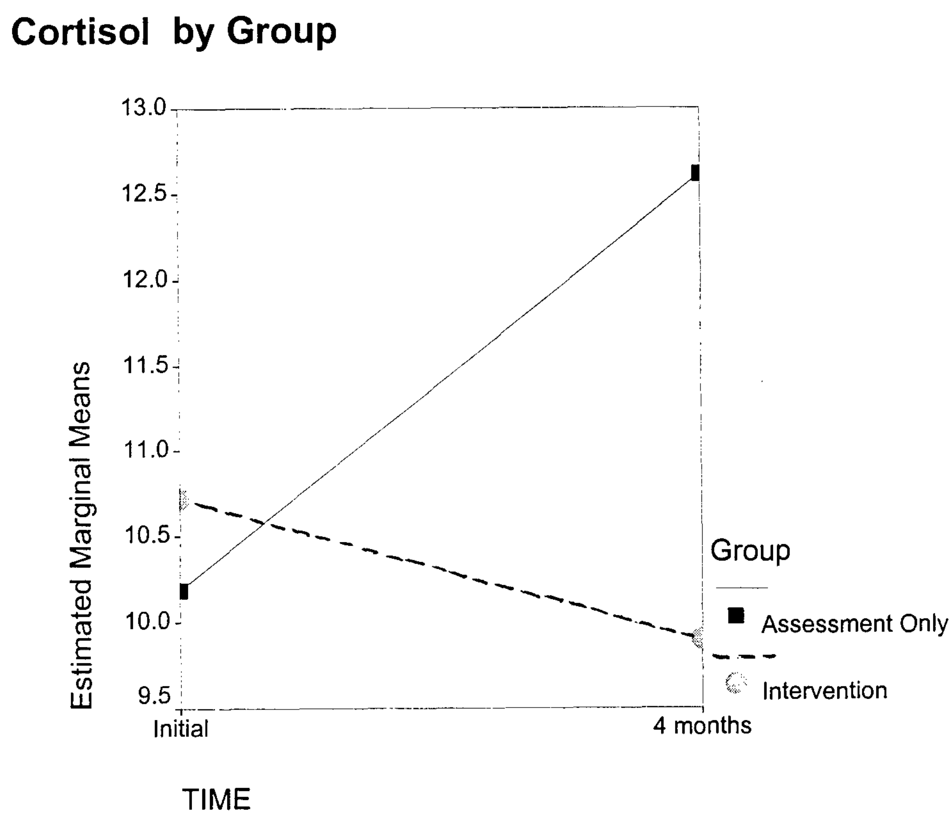
We have run analyses on all three of our hypotheses proposed for study using the initial and 4-month follow-up data. We are continuing to run analyses using the 8 and 12-month follow-up data as our endocrine data becomes available and is added to the data set. Thus, adding additional numbers will increase the reliability of our results. At this time, we are only reporting results for cortisol data.

Hypothesis 1: Do the intervention participants have significantly higher levels of social support than the assessment only subjects at 4 month follow-up?

We ran correlations between the group variable (intervention vs. assessment only) and the social support variables proposed: presence/absence of significant other (SO), social network index-total score (SNI), number of family members available (NFAM), number of friends available (NFR), number of groups (e.g., PTA, social, organizational) belong to (GRPS), perceived support from family (PSS-FA), and perceived support from friends (PSS-FR). Four of the variables (PSS-FR, NFR, GRPS, SNI) were positively correlated with the group variable at $p < .05$. To test for significant group differences over time we conducted repeated measures anovas using these variables as the outcome measure of interest. However, none of the analyses were significant at $p < .05$, all F's ≤ 3.12. Thus, at the 4-month follow-up the intervention group did not report significantly greater perceived social support or greater support availability.

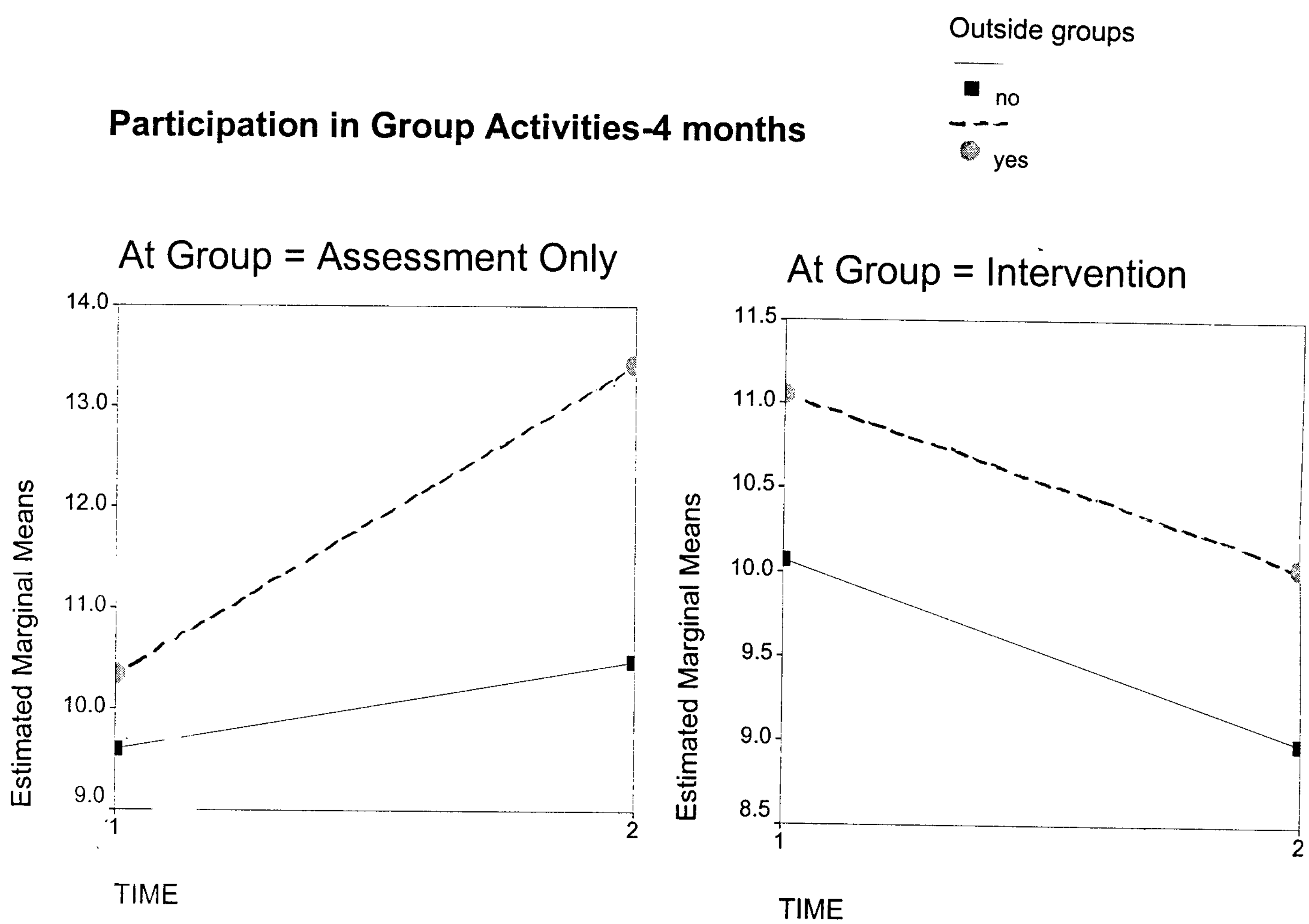
Hypothesis 2: Do the intervention participants have significantly lower levels of cortisol than the assessment only subjects?

We ran a repeated measures anova (group by time) to test for significant group differences on cortisol which was significant, $F(1, 95) = 8.69$, $p < .005$. Thus, intervention participants show lowered cortisol over time (means at initial assessment = 10.71; and 4-month follow-up = 9.90) while the assessment only subjects show a significant increase over time (means at initial assessment = 10.16; and 4-month follow-up = 12.59). This interaction over time is shown in the table below and these findings are currently under review for publication (Andersen et al.). Note: there are no significant differences on cortisol between the groups at the initial assessment.



Furthermore, psychological stress and its relationship to depressive symptoms, the number one affective concern of cancer patients was examined. In particular, the relationship of objective stressors (life events) and subjective (perceived) stress to depressive symptoms were examined. Analyses controlled for alternative hypotheses including: sociodemographics, disease, and personality factors (neuroticism). Using Hierarchical Multiple Regression, 51% of the variance in depressive symptoms was predicted, accounted for by the control variables (race, neuroticism), objective stressors (major financial difficulty and major conflict were children/grandchildren), subjective event stress (cancer stress) and subjective global stress. An examination of the squared semipartial correlations indicated that perceived global stress (10%), cancer stress (8%), and race (1%) accounted for significant unique variance in the final model. These findings are currently being reviewed for publication and the article is included in Appendix C (Golden-Kreutz et al.). Additionally, the intervention participants show significantly fewer depressive symptoms over time than the assessment only subjects (as discussed in Andersen et al., under review), also included in Appendix C.

Hypothesis 3: We wanted to test the stress buffering hypothesis of social support, that is test for an interaction between study arm (intervention vs. assessment only) and initial level of social support (high vs. low) across time (initial vs. post-treatment- 4-month follow-up) on endocrine function (e.g.., cortisol). Again, we ran repeated measures anovas (group by time by social support variable) testing for changes in cortisol levels, our outcome of interest. When necessary we converted continuous data into categorical using median splits in order to conduct analyses. While none of the analyses showed a significant three way interaction, one analysis showed two way interaction effects for both the group variable (discussed in Hypothesis 2) and for the social support variable, GRPS, $F(1, 92) = 9.37$, $p < .003$. These effects are shown in the tables below. Thus, it appears that participation in the intervention buffers women against the stressful effects (ie., increased cortisol) of other group commitments (1 or more group commitments; e.g.., social, organizational, etc.). We will test the other endocrines for this effect as the data become available.



Appendix A

Key Research Accomplishments

- *Golden-Kreutz, D.*, & Delamatre, M., Malarkey, W., & Andersen, B. (Paper for presentation at Era of Hope Meeting in Atlanta, June, 2000). Social support and endocrine function in women with breast cancer randomized to a psychological/behavioral intervention vs. assessment only.

- *Golden-Kreutz, D.*, Courtney, M.E., DiLillo, V., & Andersen, B. (Under review - Journal of Consulting and Clinical Psychology). Objective stressors vs. subjective stress and their relationship to depressive symptoms: Examining the psychological responses to cancer diagnosis and treatment.

- Andersen, B., *Golden-Kreutz, D.*, McKolanis, J., Malarkey, W., Farrar, W., DeLamatre, M., & Finn, O. (Under review - Journal of National Cancer Institute). Recovery of tumor antigen (MUC1) specific antibody following successful stress reduction in breast cancer patients randomized to a psychological intervention in addition to standard therapy.

Appendix B

Reportable Outcomes

-Manuscripts, abstracts, and presentations;

Manuscripts.

Golden-Kreutz, D., Courtney, M.E., DiLillo, V., & Andersen, B. (Under review - Journal of Consulting and Clinical Psychology). Objective stressors vs. subjective stress and their relationship to depressive symptoms: Examining the psychological responses to cancer diagnosis and treatment.

Andersen, B., *Golden-Kreutz, D.*, McKolanis, J., Malarkey, W., Farrar, W., DeLamatre, M., & Finn, O. (Under review - Journal of National Cancer Institute). Recovery of tumor antigen (MUC1) specific antibody following successful stress reduction in breast cancer patients randomized to a psychological intervention in addition to standard therapy.

Andersen, B., Farrar, W., *Golden-Kreutz, D.*, Kutz, L., MacCallum, R., Courtney, M.E., & Glaser, R. (1998). Stress alters immune responses following surgical treatment for regional breast cancer. Journal of National Cancer Institute, 90, 30-36.

Presentations.

Golden-Kreutz, D., Farrar, W., & Andersen, B. (March, 1999). Conducting clinical research with breast cancer patients: Issues of recruitment and retention. Poster presented at the 2nd Annual meeting of "Women succeeding in Science in 1999: A Multidisciplinary Poster Session" sponsored by the Association for Women in Science of Central Ohio, The Ohio State University Office of Research, College of Biological Sciences and the Battelle Endowment for Technology and Human Affairs, Columbus, Ohio.

Golden-Kreutz, D., DiLillo, V., Farrar, W., & Andersen, B. (July, 1998). The benefits of cognitive/behavioral interventions for women with breast cancer. World Congress of Behavioral and Cognitive Therapies, Acapulco, Mexico.

Andersen, B., *Golden-Kreutz, D.*, & Farrar, W. (November, 1997). Stress reduction and enhanced coping from a psychological/behavioral intervention for women with regional breast cancer: Studies from the Stress and Immunity Breast Cancer Project. Poster presented at the Department of Defense (DOD) U.S. Army Medical Research and Materiel Command Breast Cancer Research Program: An Era of Hope, Washington, D.C.

Golden-Kreutz, D., & Andersen, B. (November, 1997). Older adults in longitudinal clinical trials: Issues of recruitment and retention. The Annual Meeting of the Gerontological Society of America, Cincinnati, Ohio.

Golden-Kreutz, D., Andersen, B., Farrar, W., Courtney, M., & Armstrong, R. (August, 1997). Recruitment and retention: Conducting clinical Research with breast cancer patients. The Annual Meeting of the American Psychological Association, Chicago, Illinois.

Book Chapters.
Andersen, B., *Golden-Kreutz, D.*, & DiLillo, V. (In press). Cancer. In A.E. Kazdin (Ed.), Encyclopedia of psychology. American Psychological Association Press.

Andersen, B., *Golden-Kreutz, D.*, & DiLillo, V. (In press). Cancer, In A. Baum, T. Revenson, & J. Singer (Eds.). Handbook of Health Psychology, NY: Erlbaum.

Works in Progress.
Golden-Kreutz, D., Frierson, G., Browne, M., & Andersen, B. (For publication). Examining measurement invariance in longitudinal clinical research: A test of the Perceived Stress Scale in women with breast cancer.

Golden-Kreutz, D., & Delamatre, M., Malarkey, W., & Andersen, B. (Paper for presentation at Era of Hope Meeting in Atlanta, June, 2000). Social support and endocrine function in women with breast cancer randomized to a psychological/behavioral intervention vs. assessment only.

Golden-Kreutz, D., & Andersen, B. (Paper for presentation at Society of Behavioral Medicine in Nashville, TN, August, 2000). Impact of stressors and perceived stress on depressive symptoms in women with breast cancer.

-Patents and licenses applied for and/or issued; none

-Degrees obtained that are supported by this award; none

-Development of cell lines, tissue or serum repositories; none

-Informatics such as databases and animal models, etc.; none

-Funding applied for based on work supported by this award;
-none to date but plan to in the next year - grant proposal.

-Employment or research opportunities applied for and/or received based on experiences/training supported by this award;
-Manuscript reviewer for Health Psychology and Journal of Consulting and Clinical Psychology
-Asked to be a volunteer Professional Advisory Board Committee member to Wellness Community, a organization dedicated to the psychosocial needs of cancer patients.

Appendix C
- Published Data -

REPORTS

Stress and Immune Responses After Surgical Treatment for Regional Breast Cancer

*Barbara L. Andersen, William B. Farrar, Deanna Golden-Kreutz, Leigh Ann Kutz, Robert MacCallum, Mary Elizabeth Courtney, Ronald Glaser**

Background: **Adults who undergo chronic stress, such as the diagnosis and surgical treatment of breast cancer, often experience adjustment difficulties and important biologic effects. This stress can affect the immune system, possibly reducing the ability of individuals with cancer to resist disease progression and metastatic spread. We examined whether stress influences cellular immune responses in patients following breast cancer diagnosis and surgery.** ***Methods:*** **We studied 116 patients recently treated surgically for invasive breast cancer. Before beginning their adjuvant therapy, all subjects completed a validated questionnaire assessing the stress of being cancer patients. A 60-mL blood sample taken from each patient was subjected to a panel of natural killer (NK) cell and T-lymphocyte assays. We then developed multiple regression models to test the contribution of psychologic stress in predicting immune function. All regression equations controlled for variables that might exert short- or long-term effects on these responses, and we also ruled out other potentially confounding variables.** ***Results:*** **We found, reproducibly between and within assays, the following: 1) Stress level significantly predicted lower NK cell lysis, 2) stress level significantly predicted diminished response of NK cells to recombinant interferon gamma, and 3) stress level significantly predicted decreased proliferative response of peripheral blood lymphocytes to plant lectins and to a monoclonal antibody directed against the T-cell receptor.** ***Conclusions:*** **The data show that the physiologic effects of stress inhibit cellular immune responses that are relevant to cancer prognosis, including NK cell toxicity and T-cell responses. Additional, longitudinal studies are needed to determine the duration of these effects, their health consequences, and their biologic and/or behavioral mechanisms. [J Natl Cancer Inst 1998; 90:30–6]**

A diagnosis of cancer and cancer treatments are objective, negative events in an individual's life. Although negative events do not always produce stress and a lowered quality of life, data from many studies document severe, acute stress at cancer diagnosis *(1)* and during recovery *(2)*. The negative psychologic responses of individuals with cancer to the diagnosis and treatment are important in their own right because these responses are targets for cancer control efforts *(3,4)*. In addition, data suggest that stress responses are accompanied by nonrandom (i.e., correlated) negative changes in a broad range of immune responses. This study examines from a biobehavioral perspective whether stress influences cellular immunity in women with breast cancer after diagnosis of breast cancer and during the postsurgical period *(5)*.

Meta-analyses *(6,7)* suggest that psychologic stress and the experience of life stressors are reliably associated with negative immune alterations in noncancer subjects; i.e., "higher" levels of stress (e.g., self-reports of stress or negative affects, such as sadness or clinical diagnoses of depression) are related quantitatively and functionally to "reduced" cellular immune responses, such as lowered natural killer (NK) cell lysis. This effect has been found regularly for individuals in the midst of chronic stressors, and some of the largest responses and changes have been found for lengthy stressors and those that have interpersonal components.

Illustrative data come from Kiecolt-Glaser, Glaser, and colleagues *(8–11)*, who have followed individuals during the long, stressful experience of giving care to a spouse diagnosed with Alzheimer's disease. Not surprisingly, caregivers report high levels of distress and negative affect as they cope with their relative's difficult behavior and mental deterioration *(8)*. Moreover, these researchers have found, for example, that NK cells obtained from caregivers are less responsive to the cytokine recombinant interferon gamma (rIFN γ) and recombinant interleukin 2 (rIL-2) than are cells obtained from matched community control subjects *(9)*. In addition, these highly stressed subjects have a poorer proliferative response to mitogens *(8)*, exhibit substantial deficits in the antibody and virus-specific T-cell responses to an influenza virus vaccine *(10)*, and demonstrate stress-related defects in wound repair *(11)*.

There are fewer data on the relationship between stress and immunity among cancer patients. Levy et al. *(12)* reported on these relationships in 66 women with stage I or II breast cancer 3 months after treatment (lumpectomy or mastectomy with or without adjuvant therapy). In ad-

**Affiliations of authors:* B. L. Andersen (Department of Psychology, Institute for Behavioral Medicine Research, and Comprehensive Cancer Center), W. B. Farrar (Department of Surgery, College of Medicine, and Comprehensive Cancer Center), D. Golden-Kreutz, M. E. Courtney (Department of Psychology), L. A. Kutz (Department of Medical Microbiology and Immunology, College of Medicine), R. MacCallum (Department of Psychology and Institute for Behavioral Medicine Research), R. Glaser (Department of Medical Microbiology and Immunology, Institute for Behavioral Medicine Research, College of Medicine, and Comprehensive Cancer Center), The Ohio State University, Columbus.

Correspondence to: Barbara L. Andersen, Ph.D., Department of Psychology, The Ohio State University, 1885 Neil Ave., Columbus, OH 43210-1222. E-mail: Andersen.1@osu.edu

See "Notes" following "References."

dition to finding that estrogen receptor status predicted NK cell lysis, these researchers found that social support—a variable hypothesized to *reduce* stress—contributed significantly to a regression model predicting *higher* NK cell activity. These findings suggest that how a person responds to stress may also influence how stress, in turn, influences the immune response.

There is considerable evidence that patients with cancer express abnormal cellular immune responses; these abnormal responses have been found in patients with many different types of cancer *(13–15)*, including breast cancer *(16,17)*. Stressors are not generic, and they would not be expected to have identical physiologic outcomes. So too, the immune response involves a cascade of responses and events that can occur over time. For these reasons, we used a homogeneous breast cancer subject sample and timing of assessment to test the relationship between stress and several components of the cellular immune response, including NK cell and T-cell functions.

Women who had been diagnosed with breast cancer and who had undergone surgery for the breast cancer were studied before they began adjuvant therapy. Since we were interested in the contribution of stress in predicting an immune response above and beyond known correlates, we controlled for naturally occurring factors in our statistical analyses that affect the immune responses—specifically, age, disease stage (lymph node status), and recovery (days since surgery) *(18)*. Because the immune system contains a considerable amount of redundancy, we focused on three components that would each provide important, but complementary, information.

First, we measured NK cell lysis. We chose to measure NK cell lysis because those cells are believed to act early in the immune response and they have been demonstrated to play an important role in immune surveillance against tumors and virally infected cells *(19–21)*. Second, we measured the ability of the NK cells to respond to rIFN γ and rIL-2. It has been shown that lymphokine-activated killer (LAK) cells are highly cytotoxic against a wider variety of tumor cells than those lysed by resting NK cells *(22)*, an effect also observed in patients with breast cancer *(23)*. Finally, to obtain information on the T-cell response, we measured the response of peripheral blood leukocytes (PBLs) to two mitogens—phytohemagglutinin (PHA) and concanavalin A (Con A)—and we induced proliferation by stimulating the T cells with a monoclonal antibody (MAb) to the T-cell receptor.

Subjects and Methods

Patient Eligibility and Data Collection

Participants were 116 women who had been diagnosed with invasive breast cancer and who were surgically treated within the last 4 months but who had not yet begun adjuvant treatment. Women were from 14 to 101 days (mean = 37 days; median = 33 days) after surgery for stage II (70%) or III (30%) invasive breast cancer. We used the American Joint Committee on Cancer and the International Union Against Cancer staging system. The women ranged in age from 31 to 84 years (mean = 52 years). Recruited consecutively from mid-1994 to early 1997, the majority (82%) were being treated at a National Cancer Institute-designated, university-affiliated Comprehensive Cancer Center, and the remainder (18%) were receiving treatment at local community hospitals. All women came to the General Clinical Research Center at the university where psychologic, behavioral, and medical data were collected and a 60-mL blood sample was taken from them. Assessments were conducted between 8:00 AM and 12:00 AM to reduce diurnal variability.

Stress Measure

The Impact of Event Scale (IES) *(24)* is a standardized self-report questionnaire used to examine intrusive thoughts ("I had dreams about being a cancer patient," "Other things kept making me think about cancer") and avoidant thoughts and actions ("I tried not to talk about it," "I was aware that I still had a lot of feelings about cancer, but I didn't deal with them") concerning cancer. Fifteen items are used, and women rate each event or feeling in terms of the frequency of occurrence (i.e., "not at all," "rarely," "sometimes," and "often") during the previous 7 days. Scores range from 0 to 75. For this sample, descriptive statistics were as follows: range, 0–65, mean = 26, median = 25; and standard deviation = 15.2. The scale has satisfactory reliability with internal consistency of .78–.82 and a 2-week test–retest reliability of .79–.89, respectively. The validity of the measure is suggested by data indicating that individuals who experience involuntary, distress-related thoughts following traumatic life events are also those who suffer the greatest negative effects psychologically [e.g., *(21)*].

Immune Assays

Blood cell separation. PBLs were isolated from 60 mL of venous blood by use of Ficoll gradients (Pharmacia Biotech, Inc., Piscataway, NJ). The isolated leukocytes were then washed in calcium- and magnesium-free phosphate-buffered saline and counted on a Coulter counter (Coulter Corp., Miami, FL). Aliquots of 8 × 10^6 isolated PBLs were suspended again in 0.8 mL of RPMI-1640 medium supplemented with 10% fetal bovine serum, 0.75% sodium bicarbonate, 2 m*M* L-glutamine, and 10 μg/mL of ciprofloxacin.

Quantification of total T lymphocytes, T-cell subsets, and NK cells. Isolated PBLs were absorbed with MAbs conjugated to either fluorescein isothiocyanate or rhodamine according to the cell surface marker being studied: total T cells (CD3, fluorescein isothiocyanate), T4 subset (CD4, rhodamine), T8 subset (CD8, fluorescein isothiocyanate), and NK cells (CD56, rhodamine). All MAbs were purchased from Coulter Corp. Briefly, 0.5 × 10^6 cells were incubated with the MAb for 15 minutes at room temperature. After the incubation, the cells were fixed, and the red blood cells were lysed with Optilyse C, a buffered solution containing 1.5% formaldehyde, according to the manufacturer's instructions (Coulter Corp.). Samples were analyzed with the use of a Coulter EPICS Profile II flow cytometer as described previously *(8)*.

NK cell cytotoxicity. To determine NK cell activity, a microtiter ^{51}Cr-release cytotoxicity assay was used as described previously *(9,25)*. The target cells used were K-562 cells, an NK cell-sensitive human myeloid cell line. Target cells, labeled overnight for 16 hours with ^{51}Cr, were placed in triplicate wells of 96-well V-bottom plates, and PBLs were added, resulting in effector-to-target (E:T) cell ratios of 100:1, 50:1, 25:1, 12.5:1, and 6.25:1.

NK cell response to cytokines. Procedures for treatment of PBLs with rIFN γ and rIL-2 involved preparing isolated PBLs at a concentration of 3 × 10^6 cells/mL in complete RPMI-1640 medium and then seeding the cells into three replicate tissue culture tubes (Falcon, Becton Dickinson and Co., Lincoln Park, NJ) at 6 × 10^6 cells per tube. Cells were incubated in complete RPMI-1640 medium alone or complete medium supplemented with 250 IU/mL rINF γ or 60 IU/mL rIL-2 (Genzyme, Boston, MA). Cell suspensions were gently mixed and then incubated at 37 °C in an atmosphere of 5% CO_2 for 65 hours. For the assay, triplicate aliquots of cell suspensions were placed in wells of V-bottom plates, with E:T cell ratios of 50:1, 25:1, 12.5:1, 6.25:1, or 3.13:1. In addition, six wells with target cells and medium only and target cells with detergent (5% sodium dodecyl sulfate in phosphate-buffered saline) were prepared to determine spontaneously released chromium and maximal lysis, respectively. The plates were centrifuged at 300*g* for 5 minutes at 20 °C to bring the effector and target cells into close contact; they were then incubated at 37 °C in an atmosphere of 5% CO_2 for 5 hours. After this incubation, the plates were centrifuged at 300*g* for 5 minutes at 20 °C, 100 μL of supernatant was collected from each well, and counts per minute were determined by use of a Beckman 9000 gamma counter (Beckman Instruments, Inc., Fullerton, CA) as described previously *(9,26)*.

Blastogenic response to PHA, Con A, and MAb to the T3 receptor. The concentrations for PHA and Con A used were 2.5, 5.0, and 10.0 μg/mL. To measure the blastogenic response to the MAb to the T-cell receptor, we used the following three dilutions of the purified MAb: 32:1, 64:1, and 128:1. For all three assays isolated, PBLs seeded in triplicate at 0.5 × 10^5 per well were incubated for 68 hours at 37 °C in 96-well flat-bottomed plates and then labeled for 4 hours with MTS, i.e., 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt

(Promega Corp., Madison, WI) to measure proliferative response. Briefly, the MTS procedure is a nonradioactive calorimetric procedure that labels metabolically active cells via reduction of a colored substrate. The amount of proliferation was determined by optical density of the suspension in the well. Optical density determinations were performed by use of a Titertek Multiscan MCC microplate reader (Flow Laboratories, Inc., Finland) at a determination wavelength of 492 nm and a reference wavelength of 690 nm as has been noted *(27,28)*.

Statistical Analyses

Preliminary analyses. Before conducting the principal analyses, we checked the data for the contribution of "nuisance" variables (covariates) that could potentially be related to psychologic stress, immune outcomes, or both [*see (25)* for a discussion]. The variables examined were measures of aspirin, alcohol, caffeine, and nicotine intake; amount of sleep; plasma albumin level (as an indicator of nutritional status); incidence of recent infectious illness; and the Karnofsky performance status rating. We examined the relationships between these variables and each of the three sets of outcome variables: NK cell lysis, ability of NK cells to respond to rIFN γ and rIL-2, and the blastogenic response of PBLs to Con A, PHA, and the T3 MAb. Analysis of variance was used for the categorical independent variables, and simple correlations were used for numerically scaled independent variables.

Screening of these potential covariates involved examination of the relationships between 11 covariates and 20 dependent variables, or a total of 220 bivariate associations. Of these 220 associations, 15 were found to be statistically significant at .05 significance level. This number of significant effects is only slightly more than would be expected by chance alone (i.e., 220 × .05 = 11). Inspection of the significant relationships showed that many of them were attributable to the influence of a few outliers in the data. To be conservative, all of the regression analyses described below were run twice, once including and once excluding those covariates that had significant bivariate associations with the relevant dependent variables. In no case were results of the regression analyses significantly altered by the inclusion of the covariates. Given this fact and the consistently weak relationships of the covariates to the dependent variables, we do not report further results involving the covariates.

Principal analyses. The principal analyses assess the relationship between the IES measure of psychologic stress and the following three sets of outcome measures: 1) NK cell lysis at five E:T ratios, 2) response of NK cells to rIFN γ and rIL-2 stimulation at five E:T ratios each, and 3) the PBL blastogenic response to PHA and Con A and proliferative response to the T3 MAb at three concentrations or dilutions each.

We were interested in the role of stress in predicting these outcomes, over and above the impact of disease and recovery variables on the immune response. Thus, we chose to control for three variables: 1) age, which is associated with downregulation of the immune system, 2) disease stage, which is an indicator of the extent or burden of disease, and 3) days since surgery, which is an indicator of the degree of recovery from surgical stress and related factors (e.g., anesthesia).

Using hierarchical multiple regression *(29)*, we tested the predictive value of psychologic stress for the measured immune outcomes. This procedure enters variables in a specified sequence and, at the final step, provides a test of the variance of the dependent variable (immune outcome) due to the predictor (stress), above and beyond the contribution of the control variables (age, stage, and days since surgery). In these regression analyses, age, days since surgery, and IES were considered as numerical variables. Stage was a categorical variable with two levels: II versus III.

For all of the analyses described below, any missing data were managed by the pairwise deletion technique, wherein each bivariate association is estimated with the use of all subjects for whom measures on both variables are available. This approach allows for more complete usage of available data than do alternative procedures (e.g., listwise deletion). For all of the dependent variables except the response of NK cells to rIFN γ, the quantity of missing data was small—with never more than 10 observations missing for any bivariate association. Effective sample sizes for the regression analyses ranged from 113 for the NK cell lysis ratios to 103 for T3 MAb values. For rIFN γ measures, sample sizes varied from 85 to 49 across the range of concentrations employed.

For each analysis, we provided three regression models: models A, B, and C. Model A includes only the control (independent) variables (i.e., age, stage, and days since surgery) in predicting the immune outcome (e.g., NK cell lysis). Predictors in model A were introduced simultaneously because we had no basis for or a strong interest in investigating their effects in any particular sequence. Model B includes the three control variables as well as the psychologic stress variable (IES) in the prediction of the immune outcome. Of particular interest in this analysis was the increment in the squared multiple correlation (R^2) from model A to model B (i.e., R^2_{B-A}), indicating variance in a dependent variable (e.g., NK cell lysis) attributable to stress (IES) beyond that explained by the control predictors. In addition, the standardized regression beta (β) for the psychologic stress variable (IES) in model B (i.e., β_{Stress}) indicates the magnitude and direction of the influence of this predictor on the dependent variable. The significance of the β weight was also tested. Finally, model C indicates the contribution of psychologic stress as the lone predictor; this third model provides the simple association between psychologic stress and immune function.

Results

Analyses Predicting NK Cell Lysis

Table 1 provides the results from the three models, A, B, and C, predicting NK cell lysis. For model A, in which age, stage, and days since surgery are the independent variables, R^2_A was small and nonsignificant for every E:T ratio (all F ratios were <1.0). Because the percentage of NK cells available would influence the

Table 1. Results of regression analyses for predicting natural killer (NK) cell lysis across six effector-to-target cell (E:T) ratios

	Dependent variable: NK cell lysis at E:T ratios					
	100:1	50:1	25:1	12.5:1	6.25:1	3.125:1
Model A, R^2_A*	.005	.007	.012	.015	.020	.023
Model AA, R^2_{AA}†	.085	.148	.185	.233	.250	.241
Model B‡						
R^2_B	.135	.212	.238	.268	.275	.253
R^2_{B-AA}§	.050	.064	.053	.035	.025	.012
β_{Stress}‖	−.234	−.265	−.240	−.194	−.165	−.115
$t(df = 110)$¶	−2.462	−2.921	−2.672	−2.223	−1.892	−1.280
P	.016	.004	.008	.028	.062	.204
Model C#						
R^2_C	.067	.091	.084	.066	.056	.032
$t(df = 110)$¶	−2.826	−3.338	−3.199	−2.811	−2.558	−1.867
P	.006	.002	.002	.006	.012	.066

*Model A includes the control predictors of age, stage, and days since surgery for the immune outcome, NK cell lysis. The R^2_A is the total variance in NK cell lysis explained by these three predictors.

†Model AA includes model A variables plus the control predictor percentage of NK cells for the immune outcome, NK cell lysis. The R^2_{AA} is the total variance in NK cell lysis explained by these four predictors.

‡Model B includes model AA control variables plus the stress predictor (i.e., Impact of Event Scale [IES] score) for the immune outcome, NK cell lysis. The R^2_B is the total variance in NK cell lysis explained by the four control predictors and the stress predictor.

§R^2_{B-AA} is the increment in variance due to stress only (i.e., variance beyond that explained by the control predictors) in predicting the NK cell lysis outcome.

‖β_{Stress} is the standardized regression beta (β) for the stress variable in model B. It indicates the magnitude and direction of the influence (negative) of stress on the immune outcome.

¶df refers to the degrees of freedom in model B.

#Model C includes stress as the only predictor of the immune outcome, NK cell lysis. The R^2_C is the total variance in NK cell lysis explained by stress; this model provides the simple association between psychologic stress and immune function.

total NK cell activity as measured by lysis: we next added the percentage of NK cells, as determined by flow cytometry, into the analyses as an additional, independent control variable as shown (model AA). Across all E:T ratios, the R^2_{AA} values suggested that this variable added significant variance, as predicted, yielding R^2_{AA} values ranging from .085 to .250.

More important was the addition of the stress variable (IES) as a predictor, shown in model B. The value of R^2_B for lysis was noticeably larger than that of R^2_{AA}, and it provided a significant increment in prediction across the E:T ratios. These data indicate that the measure of psychologic stress that was used accounted for significant variance in NK cell lysis above and beyond that explained by age, stage, days since surgery, and percentage of NK cells. Moreover, the sign of the β regression coefficient for IES was negative, as predicted, indicating that an increase in measured stress was associated with a decline in NK cell lysis. The t tests for these coefficients were significant at five of the six E:T ratios. Also, no other predictor in model B had a significant regression coefficient.

We also provide the regression results when only IES was used as a predictor, eliminating the control predictors from the model (model C in Table 1). These results showed that the simple association between IES and NK cell lysis was statistically significant at five of the six E:T ratios.

Table 2. Results of regression analyses for predicting natural killer (NK) cell response to recombinant interferon gamma (rIFN γ) across five effector-to-target cell (E:T) ratios

	Dependent variable: NK cell response to rIFN γ at E:T ratios				
	50:1	25:1	12.5:1	6.25:1	3.125:1
Model A, R^2_A*	.025	.097	.080	.138	.124
Model B†					
R^2_B	.041	.151	.197	.257	.208
R^2_{B-A}‡	.016	.054	.117	.119	.084
β_{Stress}§	−.128	−.244	−.358	−.358	−.301
t	−1.104	−2.190	−3.203	−3.084	−2.083
df‖	82	81	74	65	46
P	.274	.032	.002	.004	.044
Model C¶					
R^2_C	.015	.077	.149	.149	.088
t	−1.128	−2.586	−3.581	−3.343	−2.080
df‖	82	81	74	65	46
P	.264	.012	.002	.002	.044

*Model A includes the control predictors of age, stage, and days since surgery for the immune outcome, NK cell response. The R^2_A is the total variance in NK cell response explained by these three predictors.

†Model B includes model A control variables plus the stress predictor (i.e., Impact of Event Scale [IES] score) for the immune outcome, NK cell response. The R^2_B is the total variance in NK cell response explained by the three control predictors and the stress predictor.

‡R^2_{B-A} is the increment in variance due to stress only (i.e., variance beyond that explained by the control predictors) in predicting the NK cell response.

§β_{Stress} is the standardized regression beta (β) for the stress variable in model B. It indicates the magnitude and direction of the influence (negative) of stress on the immune outcome.

‖df refers to the degrees of freedom in model B.

¶Model C includes stress as the only predictor of the immune outcome, NK cell response. The R^2_C is the total variance in NK cell response explained by stress; this model provides the simple association between psychologic stress and immune function.

Analyses Predicting Response of NK Cells to Cytokines

Results for the NK cell response to rIFN γ are provided in Table 2 and show a similar pattern. For model A, which used age, stage, and days since surgery as the independent variables, the value of R^2_A was small to moderate, ranging from .025 to .138. When stress (IES) was added to the model B regression, the R^2 values were statistically significant at all but one E:T ratio (50:1). Furthermore, the increments in the prediction due to IES, R^2_{B-A}, were significant and ranged from .054 to .119. This value reflects the proportion of variance in the cell response accounted for by stress (IES) beyond that explained by the control variables. Again, the negative weight of β for IES in model B indicated a negative influence of psychologic stress on the response of the NK cells to rIFN γ. Again, no other predictor in model B had a significant regression coefficient. Finally, the results for model C in Table 2 showed a simple association between IES and the rIFN γ response. These correlations were significant at four of the five E:T ratios; the proportions of variance accounted for were in the range of .077 to .149.

We attempted to calculate a parallel set of regressions for the response of NK cells to rIL-2. However, cells from a large proportion of the patients (62%) had no response to rIL-2. When the regressions were conducted on data obtained from the remaining patients (38%), the addition of stress (IES) in model B produced a significant R^2 value at the 25:1 E:T ratio only. It appeared that the majority of the subjects' NK cells did not respond to treatment with rIL-2.

Analyses Predicting Blastogenic Response of PBLs to Con A, PHA, and the T3 MAb

Table 3 shows regression results for the Con A and PHA blastogenic responses across three concentrations each. Because the findings are similar for both assays, they will be discussed together. For model A, which used age, stage, and days since surgery as the independent variables, the value of R^2_A for Con A ranged from .035 to .054 and was of similar magnitude for PHA, ranging from .022 to .033. Since the number of total T cells available will affect the blastogenesis values, we next added the number of T3-positive cells into the analyses as an additional, independent control variable as shown by the step model AA. Across all concentrations for each mitogen, the value of R^2_{AA} suggested that this variable added variance, yielding the R^2_{AA} values ranging from .105 to .125 for Con A and from .023 to .033 for PHA.

The addition of stress (IES) to the regression for blastogenesis added significant variance, as indicated in model B. All of the R^2 values were statistically significant. Considering the increments in R^2 due to stress (IES), these were significant and ranged from .032 to .061 for Con A and from .047 to .060 for PHA, reflecting the proportion of variance in the blastogenesis accounted for by IES beyond that explained by the control variables. Again, the negative β weights for IES in model B indicated a negative influence of psychologic stress on the blastogenic responses

Table 3. Results of regression analyses for predicting the blastogenic response to concanavalin A (Con A) and phytohemagglutinin A (PHA) across three concentrations each

	Dependent variable: blastogenic response of mitogen					
	Con A			PHA		
	10 µg/mL	5 µg/mL	2.5 µg/mL	10 µg/mL	5 µg/mL	2.5 µg/mL
Model A, R^2_A*	.035	.043	.054	.022	.024	.033
Model AA, R^2_{AA}†	.105	.125	.115	.023	.024	.033
Model B‡						
R^2_B	.166	.174	.147	.083	.074	.080
R^2_{B-AA}§	.061	.049	.032	.060	.050	.047
β_{Stress}‖	−.255	−.229	−.187	−.256	−.234	−.229
$t(df = 103)$¶	−2.668	−2.401	−1.927	−2.521	−2.299	−2.254
P	.010	.018	.058	.014	.024	.026
Model C#						
R^2_C	.053	.065	.053	.070	.054	.052
$t(df = 108)$¶	−2.443	−2.724	−2.443	−2.857	−2.489	−2.441
P	.016	.008	.016	.006	.014	.016

*Model A includes the control predictors of age, stage, and days since surgery for the immune outcome, blastogenesis. The R^2_A is the total variance in blastogenesis explained by these three predictors.

†Model AA includes model A variables plus the control predictor of number of T cells for the immune outcome, blastogenesis. The R^2_{AA} is the total variance in blastogenesis explained by these four predictors.

‡Model B includes model AA control variables plus the stress predictor (i.e., Impact of Event Scale [IES] score) for the immune outcome, blastogenesis. The R^2_B is the total variance in blastogenesis explained by the four control predictors and the stress predictor.

§R^2_{B-AA} is the increment in variance due to stress only (i.e., variance beyond that explained by the control predictors) in predicting the blastogenesis outcome.

‖β_{Stress} is the standardized regression beta (β) for the stress variable in model B. It indicates the magnitude and direction of the influence (negative) of stress on the immune outcome.

¶df refers to the degrees of freedom in model B.

#Model C includes stress as the only predictor of the immune outcome, blastogenesis. The R^2_C is the total variance in blastogenesis explained by stress; this model provides the simple association between psychologic stress and immune function.

across concentrations. Moreover, no other predictor in model B had a significant regression coefficient. Finally, results for model C in Table 3 showed a simple association between stress (IES) and the blastogenic response. These correlations were significant for each concentration of Con A and PHA.

Table 4 shows regression results for the proliferative response of T cells to three different dilutions of the T3 MAb. For model A, the control R^2 values were not significant for any dilution. Addition of number of T3-positive cells available as a control increased the variance accounted for as shown by the step model AA. The R^2_{AA} values ranged from .088 to .143. However, increments in R^2 due to the addition of stress (IES), as shown by R^2_{B-AA}, were significant, ranging from .056 to .067. This indicates that about 6% of the variance was accounted for by stress (IES) beyond that explained by the control variables. Once again, no other predictor in model B had a significant regression coefficient. Results for model C again showed the simple, significant association of stress (IES) with the response to the T3 MAb at all dilutions, with R^2_c values of .092 to .102.

Discussion

Any immune response involves a complex cascade of events that occur over time. Studies suggest that the peripheral products of stress can play numerous roles in regulating immunity, and so the effects of stress will, necessarily, be variable. Current research suggests, for example, that the acute stressors, both real stressors [e.g., parachute jumps *(30)*] and artificial stressors [e.g., experimental tasks including speech or math stress *(31)*], are correlated with the mobilization (increase) of NK cells. These changes are thought to be a result of alterations in cell trafficking. In contrast, studies of chronic stressors [e.g., bereavement, caregiving, or divorce *(7,9)*] suggest that stress can have an effect on the ability of NK cells to lyse a target cell, the ability of NK cells to respond to rIFN γ and rIL-2 *in vitro*, and other aspects of the cellular immune response.

Our results suggest that stress, as assessed via a self-report measure of intrusive and avoidant thoughts and behaviors about cancer, was related to a negative effect on NK cell lysis, the ability of NK cells to respond to two cytokines, the blastogenic response of PBLs to two mitogens, and the proliferative response to MAb T-cell receptor. These effects were inhibitory and of similar magnitude (i.e., reliable), both between the assays and within an assay (i.e., across E:T ratios and mitogen concentrations). The analyses controlled for variables that might also be expected to exert short-term or long-term effects on immunity—such as age, stage of disease, and days since surgery—and ruled out other potentially confounding variables (e.g., nutritional status) that might also be influential. These controls reduced the plausibility of alternative, rival hypotheses for these consistent findings.

It is recognized that NK cells mediate natural immunity, but some researchers *(32)* suggest that their role in health generally has been underestimated. For example, there is evidence to suggest that the NK cells participate either directly or indirectly in multiple developmental, regulatory, and communication networks of the immune system. Furthermore, NK cells are efficient effector cells that not only are equipped for cell killing, but also are capable of rapid responses to exogenous or endogenous signals by producing cytokines and other factors involved in interactions between immune and nonimmune cells *(20)*.

The ability to spontaneously lyse a broad range of infected cells or tumor cells is the best known functional attribute of NK cells *(20,22)*. Consistent with previous reports, these data suggest that stress may impair this important process. Our findings highlight the specific effect of cancer stress on immune function, whereas prior data obtained by Levy et al. *(33)* had suggested that women's reports of fatigue were related to lower levels of NK cell lysis. Chronically low levels of NK cell activity occur in patients with cancer, particularly when there are large tumor burdens or disseminated metastases *(32)*. In general, patients with low NK cell activity appear to be at higher risk for infections, to have more prolonged diseases, or to suffer more severe symptoms

Table 4. Results of regression analyses for predicting proliferative response of peripheral blood leukocytes to a monoclonal antibody to T-cell receptor (T3) across three dilutions

	Dependent variable: proliferative response at dilutions		
	128:1	64:1	32:1
Model A, R^2_A*	.026	.052	.064
Model AA, R^2_{AA}†	.088	.104	.143
Model B‡			
R^2_B	.155	.160	.200
R^2_{B-AA}§	.067	.056	.057
β_{Stress}‖	−.273	−.249	−.252
$t(df = 101)$¶	−2.747	−2.514	−2.604
P	.008	.014	.012
Model C#			
R^2_C	.102	.092	.094
$t(df = 101)$¶	−3.452	−3.255	−3.307
P	.002	.002	.002

*Model A includes the control predictors of age, stage, and days since surgery for the immune outcome, proliferative response. The R^2_A is the total variance in proliferation explained by these three predictors.

†Model AA includes model A variables plus the control predictor of number of T cells for the immune outcome, proliferation. The R^2_{AA} is the total variance in proliferation explained by these four predictors.

‡Model B includes model AA control variables plus the stress predictor (i.e., Impact of Event Scale [IES] score) for the immune outcome, proliferation. The R^2_B is the total variance in proliferation explained by the four control predictors and the stress predictor.

§R^2_{B-AA} is the increment in variance due to stress only (i.e., variance beyond that explained by the control predictors) in predicting the proliferation outcome.

‖β_{Stress} is the standardized beta (β) for the stress variable in model B. It indicates the magnitude and direction of the influence (negative) of stress on the immune outcome.

¶df refers to the degrees of freedom in model B.

#Model C includes stress as the only predictor of the immune outcome, proliferation. The R^2_C is the total variance in proliferation explained by stress; this model provides the simple association between psychologic stress and immune function.

than patients whose NK cell activity remains normal *(32,34)*.

A variety of biologic response modifiers are known to increase the activation, proliferation, or cytotoxicity of NK cells *(20)*. Among the best known activators of NK cells are IL-2 and IFN γ. Our data show that the physiologic changes associated with psychologic stress inhibited NK cell lysis. Stress also affected the ability of NK cells to respond to rIFN γ, a finding that is consistent with two previous reports involving another life stressor (i.e., caregiving for a spouse with Alzheimer's disease *(9,26)*]. It is interesting that NK cells from 62% of the women did not respond to rIL-2. In subsequent analyses comparing women who did have an rIL-2 response with those who did not, no stress or disease variable differentiated the two groups. Further studies will need to be performed to explore this result, although it is possible that the lack of responsiveness of NK cells to rIL-2 may be due to an overproduction of prostaglandin E_2 by monocytes. It has been suggested that in breast cancer patients prostaglandin E_2 decreases IL-2 production in effector cell populations, resulting in the down-regulation of the expression of the IL-2 receptor on NK cells *(23)*. Follow-up studies will need to pursue and clarify this difference in cytokine responses.

It has been shown that the ability of PBLs to respond to PHA is reduced, in general, in cancer patients *(35)*; this lowered response is related to tumor burden and declines in the ability of PBLs to respond to PHA with disease progression *(36)*. The negative effect of stress on blastogenesis was replicated in this study across two mitogens, PHA and Con A, as well as in the response of T cells to an MAb against the T-cell receptor. These findings are consistent with correlational and experimental studies indicating that stress impairs the blastogenic response of PBLs to mitogens and virus-specific T-cell responses *(8,10,37–39)*. Mitogen-induced proliferation has been used to indicate the immune system's ability to respond to antigens from pathogens. Chronically stressed, but healthy, individuals showing decrements in the cellular immune response (including NK cell lysis and the response of the PBLs to mitogens) subsequently reported a higher incidence of infectious illnesses *(8)*. If this effect is reliable, these data would suggest that cancer patients who experience high levels of stress, lowered levels of responsive T lymphocytes, and decreased NK cell function may be at greater risk for infectious illnesses as they begin adjuvant therapy.

It is interesting that evidence is accumulating to suggest that psychologic and/or behavioral stress reduction interventions may *enhance* certain aspects of the cellular immune response, including NK cell lysis. In an early investigation, Kiecolt-Glaser et al. *(40)* studied 61 healthy adults living in a retirement home. After receiving 1 month of training in progressive muscle relaxation, the subjects showed evidence of a 30% increase in NK cell lysis in comparison with those who received no treatment or only social contact. Fawzy et al. *(41)* studied 61 patients with melanoma and reported that, 6 months after treatment, subjects receiving intervention had significantly higher levels of IFN alfa-augmented NK cell activity than those who received no treatment. These data suggest that, if behavioral interventions can reduce stress and enhance the cellular immune response, then health outcomes might improve.

In conclusion, these data show a down-regulation of different aspects of the cellular immune response associated with the psychologic stress that accompanies the diagnosis and initial surgical treatment of cancer. We note that these study participants are part of a larger effort testing the biobehavioral aspects of stress, immunity, and disease course *(5)*. It will be important to document the longitudinal nature of these findings, and future studies will provide such data. Moreover, half of the women who participated have been randomly assigned to receive a psychologic/behavioral intervention specifically designed to reduce stress, enhance quality of life, and test for the biologic mechanism—such as immune responses—that may mediate any positive effects of stress reduction on health and disease outcomes.

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tate cancer screening. Arnauld Villers, M.D., Ph.D., a urologist from the Hospital Purpan in Toulouse, France, said he expects the agency to allow general practitioners to recommend PSA testing for men 50 to 75 years of age within the next few months. Prostate cancer gained importance among the French public after former president Francois Mitterrand's diagnosis and subsequent death from the disease in 1996.

Participation rates in the screening trials vary partly due to randomization methods. Some of the trials randomize entire geographic populations. Then men in one area are offered screening. Acceptance of this offer is highest in Finland at 70%; Italy and Sweden are at 60%.

Other trials recruit men prior to randomization and seek to maximize participation so that men in the trial are more typical of the general population. With this approach, the Netherlands has 46% participation.

The study that is based in Antwerp, Belgium, managed to boost its participation rate from 18% to 34% by visiting the homes of men who are eligible to participate. Spain has reached only 23%, and that study's leaders don't expect participation to improve, due to the population's overall fear of detecting illness.

Strength from Diversity

Although the studies follow a core protocol (they must use PSA, employ one of two valid randomization approaches, ascertain prostate cancer mortality in both arms of the study, and apply quality control standards for application of the screening tests), they contain deliberate variations (J Natl Cancer Inst, June 21, 1995;87:868-871). They vary in the number of years between screenings, in the PSA measure that indicates the need for further testing, and in the screening tests provided along with PSA (they may or may not provide digital rectal exam or transrectal ultrasound.). Finally, the treatment options offered depend on each patient's urologist.

This lack of uniformity among the protocols is, technically speaking, an epidemiologists' nightmare. But Freda Alexander, Ph.D., of the University of Edinburgh, Scotland, chair of the ERSPC Epidemiology Committee, used an example to point out its added value. "We could just go with very frequent screenings to get the maximum effect, but that doesn't tell us how well much cheaper screening works." So some centers are using a 1-year screening interval, while others are waiting as long as 4 years between screenings.

Schröder agreed. "There will be a wealth of information coming from [the combined studies] concerning the optimization of the use of screening tests, the types of cancer detected at screening, and prognostic factor analysis that may allow greater selectivity of screening procedures in the future, with proper identification of the type of tumor that may benefit from early treatment."

To avoid contamination of the control group and because the study is looking for differences in mortality, study group members have committed to delay publishing endpoint data until 10-year followup is completed. But, Alexander added, "If evidence accrues that screening might influence shorter-term conditions, the ERSPC management committee could change that policy."

— *Cori Vanchieri*

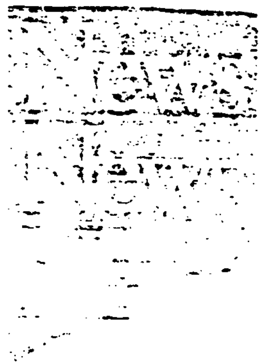
Stress Reduction: Three Trials Test Its Impact on Breast Cancer Progression

Does psychological stress play a role in cancer progression and can reducing stress slow tumor growth? Some answers could be available soon after the year 2000 to this question, which has intrigued mental health specialists for several decades.

Up to now, the field of psychoneuroimmunology has yielded relatively little data related to cancer. In the area of infectious diseases, particularly colds, researchers have found a variety of links between psychological stress and the immune system. A few investigators have looked specifically at cancer patients and how the stress of diagnosis and treatment may affect immune response. Only a very few have ever designed an intervention to see whether stress reduction can improve immune function and slow cancer progression.


Dr. Barbara Andersen

Now, three such studies are under way, all randomized, controlled trials of support-group interventions with breast cancer patients. None of the trials has data on tumor recurrence or survival yet. But early findings from one of them, reported on page 30, support the hypothesis that cancer-related stress is associated with cellular immune responses that may play a role in tumor growth.



Barbara Andersen, Ph.D., and colleagues at Ohio State University, Columbus, report that baseline measures of stress, specific to the diagnosis of cancer, were linked to levels of natural killer cell activity, T-cell responses, and other cellular responses "relevant to cancer prognosis."

It's still a big step from this finding to the question that Andersen would most like to answer: Can a stress reduction intervention influence cancer progression? But her larger study, plus two others now in progress in the United States and Canada, may help provide that answer over the next 6 years.

Andersen's larger study at Ohio State will involve 235 women with stage II or III breast cancer who are randomized, after surgery and before adjuvant therapy, into two groups, one of which will attend support groups for a year. The group sessions empasize both emotional support and education on, for instance, coping strategies.

All participants are assessed, first at enrollment and then 5 years following randomization to determine stress levels, cellular immune responses, and cancer recurrence. As of Dec. 1, 1997, 160 patients had been accrued. Recruitment should be completed in 1998, Andersen said, and results could be available in about 6 years.

While the step from reducing stress to reducing recurrence rates seems a giant one, the hypothesis has some evidence to back it. In the late 1980s, David Spiegel, M.D., a psychiatrist at Stanford University, discovered that breast cancer patients who received psychosocial support had better survival rates than patients in a control group who received no formal intervention.

Spiegel said he and his colleagues had set out to study the impact of a particular form of support on quality of life. They had not intended to look at survival. But after 10 years, they found that the 50 women in the support group (designed to encourage full "emotional expressiveness" about the cancer and allow patients to confront their feelings about the disease) had survival rates nearly twice those of the 36 patients in the control group. Mean survival for the intervention group was 36.6 months from the time of randomization compared with 18.9 months for the control group.

A few other small studies have had contradictory results. Most frequently cited is a randomized controlled trial at the University of California, Los Angeles, where Fawzy I. Fawzy, M.D., found that a psychosocial intervention was associated with longer survival in melanoma patients.

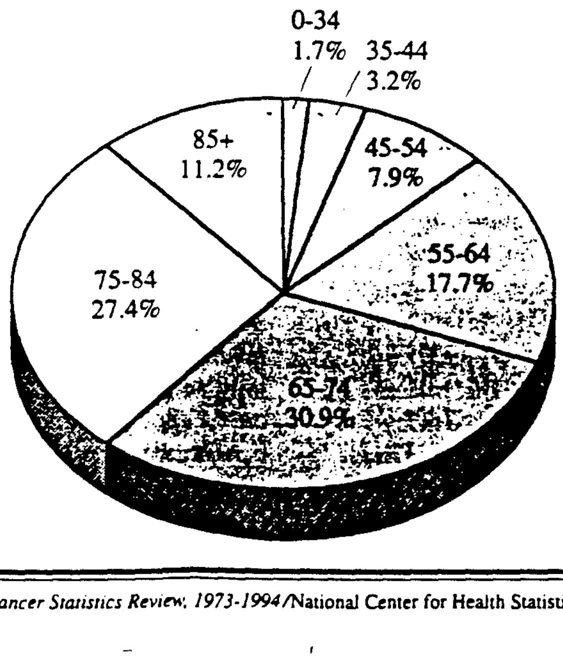
The other U.S. trial looking at stress reduction, immune factors, and cancer

Stat Bite

Age Distribution of Cancer Deaths in the United States

While cancer mortality has begun to decline in the United States, it is estimated that about 560,000 Americans died of the disease in 1997. Because cancer more often occurs in older age groups, more than two-thirds of cancer deaths occur after age 64.

Percent of cancer deaths by age group, all sites, 1990-1994



Source: *SEER Cancer Statistics Review, 1973-1994*/National Center for Health Statistics public use tapes.

progression is under way at Stanford where Spiegel and colleagues are replicating the earlier study with a larger group. Initiated in 1990, the trial has 125 participants who were randomized into two groups, one of which attended support sessions.

Now about three-quarters of the way through a 10-year followup, the investigators are monitoring endocrine and cellular markers of immune function, such as cortisol levels and natural killer cell activity, as well as recurrence and survival rates. Spiegel said they expect to have some preliminary results published later this year, and final results, including survival data, could be ready around the year 2000.

A third trial on stress reduction and cancer progression is taking place in Canada at seven different sites. Led by Pamela Goodwin, M.D. at Mount Sinai Hospital, Toronto, the trial is replicating Speigel's intervention with 235 women. Goodwin said this study should have completed recruitment by the end of 1997 and that results, including survival data, could be available around 2000.

Controversy Continues

A major hypothesis in all three studies — that stress reduction can alter immune function in a way that influences cancer progression — is a controversial one, said Sheldon Cohen, Ph.D. and Bruce Rabin, M.D., University of Pittsburgh, in their editorial on page ___. There is too little known, for one thing, about the type and magnitude of the immune responses that influence cancer progression, they say.

Another problem in studying the role of psychosocial interventions are the number and complexity of factors that might independently influence immune responses and cancer progression. All three trials now in progress are controlling for known prognostic factors, such as the extent of lymph node involvement and whether the tumor cells had estrogen receptors. But numerous other factors could play a role, including the immunosuppressive effects of cancer treatment, the details of which are not completely known.

Another point noted by Cohen and Rabin — and one that turns up repeatedly in the literature on stress reduction and cancer survival — is that a support group could influence disease progression by means other than the stress reduction/immune response mechanism. For instance, supportive interventions might work because they encourage treatment compliance.

Spiegel said that he and colleagues examined this issue in their earlier study by reviewing participants' medical records. They found no difference in treatment that could account for the difference in survival rates. For that trial, "we've pretty much ruled out differences in treatment as an explanation," he said.

However, the impact of intervention on compliance with treatment is still an unknown. One hypothesis being tested in the Canadian study, said Goodwin, is that the psychosocial intervention improves survival by encouraging compliance. The Ohio State researchers are also looking at medical treatment, collecting data not only on prescribed treatment but also on the chemotherapy doses that each patient actually receives.

It is a key issue, Andersen said. "This is something we are looking at very closely."

— *Caroline McNeil*

To Build a Better Mousetrap, Use Human Parts

Historically disappointing results with mouse-based monoclonal antibodies (MAbs) have biased many clinicians against this approach to treating human diseases. Now, re-engineered antibodies are ready for a comeback, thanks to the persistence of a few researchers who were unwilling to abandon the idea.

One MAb, IDEC-C2B8 or rituximab, recently was approved by the Food and Drug Administration for treatment of a type of non-Hodgkin's lymphoma (see sidebar). Several others, such as HER2 for breast cancer and A33 and anti-EGP40 for colorectal cancer are in clinical trials. And at least two dozen other MAbs are in various stages of clinical testing in the cancer setting.

Such signs of progress have rekindled hope in those researchers who


Dr. Thomas A. Waldmann

have continued over the past several decades to explore the basic MAb concept — that an antibody injected into a cancer patient could seek out a specific antigen on cancer cells, bind to that antigen, and activate the body's immune system to kill with great specificity only the cancer cells.

The breakthrough that turned that vision into clinical reality, according to Thomas A. Waldmann, M.D., chief of the metabolism branch at the National Cancer

Appendix C
- Unpublished Data -
Under review

Running head: STRESS MEASUREMENT AND CANCER

Objective stressors vs. subjective stress and their relationship to depressive symptoms: Examining the psychological responses to cancer diagnosis and treatment

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Vicki G. DiLillo, and Barbara L. Andersen
The Ohio State University

Key words: Stress, depressive symptoms, breast cancer

Abstract

The relationship of objective stressors (life events) and subjective (perceived) stress to depressive symptoms was examined. These relationships were examined using a clinically relevant paradigm, stressed individuals who were vulnerable to the experience of depressive symptoms, namely women recently diagnosed and surgically treated for breast cancer. Analyses controlled for alternative hypotheses including: sociodemographic, disease, and personality factors. Using Hierarchical Multiple Regression, 51% of the variance in depressive symptoms was predicted, accounted for by the control variables (race, neuroticism), objective stressors (major financial difficulty and major conflict with children/grandchildren), subjective event stress (cancer stress; IES), and subjective global stress (PSS-10). An examination of the squared semipartial correlations indicated that perceived stress (10%), cancer stress (8%), and race (1%) accounted for significant unique variance in the final model. While "stress" measures are correlated, these findings indicate that subjective measures of stress were uniquely better predictors of depressive symptoms than objective measures. Further, a global perception of stress was a stronger predictor than perceived stress for a specific event. Implications for the use of such measures with stressed populations, who are often vulnerable to other comorbid difficulties such as depression, are discussed.

Objective stressors vs. subjective stress and their relationship to depressive symptoms:

Examining the psychological responses to cancer diagnosis and treatment

Stress, whether measured objectively or subjectively, is associated with poor psychological and physical outcomes across a variety of groups (e.g., college students and adults in community smoking cessation program: Cohen, Kamarck, & Mermelstein, 1983; adult psychiatric patients: Hewitt, Flett, & Mosher, 1992; highway patrol officers: Hills & Norvell, 1991). While studies may include both objective and subjective measures of stress, few studies have examined their relative associations to outcomes (Cohen et al., 1983; Cohen & Williamson, 1986; Hills & Norvell, 1991; Pbert, Doerfler, & DeCosimo, 1992). Such comparisons would be important because an examination of the "predictive validities of objective and subjective stress measures" would clarify the role of perceptions in the relationship between stress and outcomes (e.g., psychological functioning; p. 386, Cohen et al., 1983). The present study is an examination of the relative explanatory power of three different types of stress measures in relation to depressive symptomatology. This examination was conducted using an important and naturally occuring stressor - cancer diagnosis and treatment. Individuals are signficantly stressed at the time of diagnosis and treatment, and depressive symptoms are the most common affective symptoms reported (e.g., Derogatis et al., 1983; See Tope, Ahles, & Silverfarb, 1993, and van't Spiker, Trijsburg, & Duivenvoorden, 1997 for reviews).

Conceptualization and measurement of stress

The conceptualization and methodology in research on self-reported stress has evolved over the last 20 years (See Table 1 for an overview of the measures available). Early research on the psychological effects of stress arose from the notion that difficult life events (unemployment, death of a relative, etc.) are stressors (Cobb & Kasl, 1977; Stroebe, Stroebe, Gergen, & Gergen, 1982). Studies focused on the objective assessment of stress, the presence/absence, total number, or type of stressful life events experienced during a specified period of time (e.g., during the last year). Such measures did not involve evaluations, feelings, or cognitions associated with the events. These measures appeared important, as the data indicated that the number and/or type of life events were associated with psychopathology including depression (Finlay-Jones & Brown, 1981; Warheit, 1979), anxiety (Finlay-Jones & Brown, 1981; Manfro et al., 1996), anorexia nervosa (Horesh et al., 1995), and psychosis (Bebbington et al., 1993). Additionally, a greater number of events have been related to poorer health outcomes (Baum, Gatchel, & Schaffer, 1983; Dohrenwend & Dohrenwend, 1974; 1978; Holmes & Rahe, 1967).

Despite these data, objective measures were criticized as they did not account for individual differences in response to stressors. It was reasoned that a person's response to stressors is not based completely on the type or number of events, but also involves cognitive appraisal processes as well (Cohen et al., 1983; Lazarus & Folkman, 1984). For these latter processes, subjective measures of stress were introduced. Subjective measures assess perceptions of stress during a specific time period (e.g., the past week or month) and are of two basic types: event specific or global. Event specific measures ask the person how stressful a given situation (e.g., occupation) or event (e.g., bereavement, cancer diagnosis) is perceived to be. Event specific measures can be: 1) a one-item measure of how stressful a single event/situation is perceived, 2) a total score across items (stressors), or 3) a measure with several items assessing different aspects of a single event/situation. Alternatively, global subjective measures do not reference specific events/situations, but instead ask individuals if they perceive their lives as generally stressful.

When the differential predictive power of objective versus subjective measures have been compared, subjective measures have consistently been better predictors of psychological and physical outcomes (Cohen et al., 1983; Martin, Kazarian, & Breiter, 1995; Pbert et al., 1992; Sarason, Johnson, & Siegel, 1978; Vinokur & Selzer, 1975). For example, Cohen and colleagues (1983) offered a global measure of preceived stress, the Perceived Stress Scale (PSS), contending that such a measure would provide a better measure of stress than would objective stressors or even subjective ratings of events. They raised three concerns with the other methods. First, the predictive power of subjective ratings of events relative to objective measures of events appeared to be small. Second, they suggested that people err in the attributions they make about their stress. For example, it is more common for individuals to associate stress with a current, identifiable event (e.g., recent death of relative, divorce) than with chronic circumstances (e.g., financial problems, marital distress). Third, they asserted that responses to an event are better reflected by global stress measures than stress associated with specific events or situations. For instance, a person's response to an event does not occur in isolation but in the context of other factors (socioeconomic status, personality, etc.) and, of course, all of these factors may contribute to one's perception of stress. Research has suggested global subjective stress ratings may be a better predictor of psychological outcomes than either objective or event specific measures of stressors (Cohen et al., 1983; Kuiper, Olinger, & Lyons, 1986; Martin et al., 1995; Pbert et al. 1992).

<u>An example: Assessment of stress in cancer populations</u>

Studies have examined life events as predictors of cancer risk (e.g., Cooper and Faragher, 1993; Ginsberg, Price, Ingram, & Nottage, 1996; Ramirez et al., 1989; Roberts, Newcomb, Trentham-Dietz, & Storer, 1996), but few studies have examined the relationship between life events and the stress of diagnosis and treatment. The available data suggest that an increased number of recent life events are positively related to distress (Bukberg, Penman, & Holland, 1984; Grassi, Malacarne, Maestri, & Ramelli, 1997; & VanServellen, Sarna, Padilla, & Brecht, 1996).

Early studies documented acute distress experienced at diagnosis (e.g., Andersen, Anderson, & deProsse, 1989; Weisman & Worden, 1976), but contemporary studies suggest that cancer diagnosis and treatment may, in fact, constitute a “traumatic event” (4th ed; DSM-IV: American Psychiatric Association, 1994; Cordova et al., 1995; Andrykowski, Cordova, Miller, & Studts, 1998). As a result, existing measures of traumatic stress such as the Impact of Events Scale (IES; Horowitz, Wilner, & Alvarez, 1979) have been modified for cancer populations (changing the word “event" on the original scale to "disease" or "cancer"). Much of the research examining cancer stress has, in fact, used the IES to examine the frequency or severity of trauma-related intrusive cognitions and avoidant behaviors, and their relationships to psychological outcomes (Baider & De-Nour, 1997; Cordova et al., 1995; Schwartz, Lerman, Miller, Daly, & Masny, 1995). There are consistent positive relationships between intrusive thoughts and severity of psychological distress (e.g., patients at high risk for cancer, Schwartz et al., 1995), and weaker or no relationship between avoidant thoughts/behaviors and psychological distress (breast cancer patients, Baider & De-Nour, 1997 and Cordova et al., 1995; parents of pediatric cancer patients, Hall & Baum, 1995).

In contrast to the use of subjective ratings of the cancer “event,” fewer cancer studies have included globally perceived stress measures (Bull & Drotar, 1991; Schulz et al., 1995; Varni et al., 1994). One of these exceptions is a study by Varni and colleagues (1994) who found that higher perceived global stress predicted increased psychological distress (e.g., depression and anxiety) in adolescent survivors of pediatric cancer. In comparing the three methodologies, the research focus has been on objective stressors and subjective ratings of the cancer stressor, with fewer studies examining subjective global stress.

A closer look at the stress of cancer diagnosis and treatment

The diagnosis and treatment of cancer are significant life stressors and their negative impact on psychological well-being and quality of life has been thoroughly discussed elsewhere (e.g., Andersen, 1992; Andersen, Kiecolt-Glaser, & Glaser, 1994). Weisman and Worden (1976), for example, noted that the diagnosis of cancer produces an "existential plight," meaning that the news brings shock, disbelief, and emotional turmoil. Sadness, fear, and confusion can characterize the diagnostic period. The majority of people diagnosed with cancer will not only be distressed but the experience will also result in some degree of depressive symptomatology. In fact, 50% of patients will meet the American Psychiatric Association's criteria for psychiatric diagnosis, with the most common being adjustment disorder (Derogatis et al., 1983). Breast cancer alone (one of the most commonly diagnosed cancers in women with over 175,000 new cases yearly in the United States; Landis, Murray, Bolden, & Wingo, 1999), annually yields a subset of women numbering close to 90,000 who may be at risk for clinically significant depressive symptoms due to their cancer experience.

In addition to distress, other variables also may contribute to higher rates of depressive symptoms in the context of cancer, such as sociodemographic, disease, or personality characteristics. Again, we consider the case of breast cancer. Sociodemographic variables (e.g., age, race, SES) are correlated with breast cancer incidence and/or mortality (Faggiano, Partanen, Kogevinas, & Boffetta, 1997; Landis et al., 1999; Schrijvers & Mackenback, 1994), but their relationship to depressive symptoms is inconclusive (Carver et al., 1994; Dean, 1987; Hughson, Cooper, McArdle, & Smith, 1988; Lee et al. 1992; Levy et al., 1992; Pinder et al., 1993; Stanton & Snider, 1993). Disease variables such as stage of disease, type of surgical treatment, and time since diagnosis/treatment are related, in general, to psychological outcomes in women with breast cancer. In particular, data suggest that women with more advanced disease may have more severe depressive symptoms (e.g., Glanz & Lerman, 1992; Pinder et al., 1993; Stanton & Snider, 1993). Personality variables, most commonly neuroticism, have also been examined. While positive associations between neuroticism and negative affective states (e.g., depressive symptoms) have been found in heterogeneous cancer groups (Jenkins, May, & Hughes, 1991; VanderZee, Buunk, & Sanderman, 1996), the specificity with regards to breast cancer patients needs to be investigated. This potential relationship may be particularly important as neuroticism is consistently associated with psychological distress in other non-cancer populations (e.g., Clark, Watson, & Minneka, 1994; Watson, 1988), and has been proposed as a risk factor for psychological distress (Clark et al., 1994; Watson & Pennebaker, 1989).

Aim of the research

The present study tests the relative explanatory power of measures of objective stressors and subjective stress in the prediction of depressive symptoms. We test this question in an important and naturally occurring paradigm - cancer diagnois and treatment. We choose women recently diagnosed and surgically treated for breast cancer due to the psychologic and biologic distress associated with this stressor (Andersen et al., 1998). Depressive symptoms were the predicted outcome because of its prevalence in this population (van't Spiker et al., 1997). The relationship of objective stressors and subjective stress to depressive symptoms is examined after variables associated with depressive symptoms - sociodemographics, disease characteristics, and the personality trait, neuroticism, were controlled. Even though these variables may be important for further study, they were not the focus of the present study. And so, we controlled for these variables because of their potential confouding relationship with depressive symptoms.

We tested two hypotheses. First, we anticipated that subjective measures of stress would be better predictors of depressive symptoms than objective measures. To enhance the rigor of this comparison we selected high frequency objective stressors important to a woman with breast cancer (e.g., divorce, financial difficulty). Second, globally measured stress was predicted to have a stronger relationship with depressive symptoms than was the stress associated with specific events, namely life event stress and cancer stress. In summary, we explore the relationship among "stress" measures in predicting depressive symptoms for a common, real-life stressor.

Method

Participants

Women newly diagnosed and treated for regional breast cancer were studied (N = 166). Participants were from a larger prospective, longitudinal study (The Stress and Immunity Breast Cancer Project).[1] See Table 2 for sociodemographic and cancer-specific disease characteristics of the sample.

Procedures

Participants were accrued from mid-1994 to mid-1998. The women were recruited primarily from physician's offices at a National Cancer Institute-designated university-affiliated Comprehensive Cancer Center (84%, n = 139). Other participants were self referrals from newspaper advertisements, press releases, and project flyers (16%; n = 27). At the time of assessment, all participants had been surgically treated (lumpectomy or mastectomy) within the preceding 3 months but had not yet begun adjuvant treatment (e.g., chemotherapy, radiation). Psychological, behavioral, and medical/treatment information were collected with an interview and other data collection conducted at the University's General Clinical Research Center or the breast cancer clinic. Disease and surgery information were verified using information from the women's medical charts/reports and confirmed with primary care providers. All women were paid $20.00 for their participation.

Measures

Control variables

Sociodemographics, disease variables, and personality. Three classes of variables were controlled. The sociodemographic variables included: age, race (White vs. minority status), partner status (yes vs. no), education (years), and family income (dollars per year). The disease variables examined were stage of disease (stage II vs. stage III), extent of surgery (lumpectomy vs. mastectomy), and time since surgery (in days). The personality variable was assessed with the neuroticism factor from Goldberg's Big-Five Factor Measure (1992). Items from this factor were extracted from a factor analysis with the present sample as suggested by Goldberg (personal communication, 1996). Confirming the items as originally provided (Goldberg, 1992), the factor included 16 trait adjectives, 9 positive for the trait of neuroticism (e.g., irritable, nervous) and 7 negative (e.g., even-tempered, at-ease). Each woman rated the extent to which these trait adjectives described her, as compared to others of the same sex and age, on a nine-point Likert scale from "extremely inaccurate" to "extremely accurate." Total scores range from -63.0 to 81.0, with higher scores indicating stronger trait neuroticism. For the present study, the average neuroticism score of the participants was 4.3 (SD = 17; range -32 to 46) and coefficient alpha reliability was .91.

Predictor variables

Objective stressors (life events) and life event stress. The event scale used was adapted from that in the Women's Health Initiative study (Matthews et al., 1997). Participants were asked to indicate if they had experienced any of five stressful life events, ones identified as being stressful for women (see Table 3). By assessing the occurrence of life events over the previous year, the chronic or long-term impact of life events on later adjustment is assessed. If an event occurred, women then rated how emotionally upsetting the event was (e.g., 3=very much, 2=moderately, 1=not much). Three scores were calculated: presence versus absence of each event (0=not occurred, 1=occurred), the total number of events reported (range 0-5), and the sum of the distress ratings (total range for 5 events, 0-15).

Subjective cancer stress. The IES (Horowitz et al., 1979) is a standardized self-report measure used to examine cognitions involving the re-experiencing (intrusion) and denial of thoughts and avoidant behaviors (avoidance) related to trauma (Miller, 1996). Fifteen items are used, seven for the intrusive subscale (e.g., "I had trouble falling or staying asleep because pictures or thoughts about cancer or having cancer treatment came into my mind") and eight items for the avoidant subscale (e.g., "I tried not to think about it"). Consistent with previous research, the word "event" was changed to "cancer." Women rated each item as experienced in the previous week, using a 4-point Likert scale (not at all=0, rarely=1, sometimes=3, and often=5). Three scores are obtained from the IES, a total score (IES-T) and intrusion (IES-I) and avoidance (IES-A) subscale scores. Total scores can range from 0 to 75 with higher scores indicating increased severity of cancer-related stress. In the present sample the coefficient alpha reliability was .87, consistent with other studies reporting reliabilities of .78-.83 (Cordova et al. 1995, Horowitz et al., 1979; Schwartz et al., 1995).

Subjective global stress. The PSS (Cohen et al., 1983), a measure of perceived stress, is a standardized self-report questionnaire used to determine the extent to which a person judges her/his life to be unpredictable, uncontrollable, and overloading (Cohen et al., 1983). Based on Cohen and Williamson's (1986) recommendation, the ten item PSS-10 was used for its improved internal reliability and factor structure over other versions of the PSS. Examples of the questions include: "How often have you felt nervous or stressed" and "How often have you felt confident about your ability to handle your personal problems." Women rated how often they experienced the above feelings in the past month on a 5-point Likert scale (from never=1 to very often=5). Total scores range from 0 to 40 and higher scores indicate greater overall stress. Coefficient alpha reliability was .86 in the present sample and ranges from .75 to .86 in the literature (Cohen et al., 1983; Hewitt et al., 1992; Martin et al., 1995; & Pbert et al., 1992).

Outcome variable

Depressive symptoms. The short form (IOWA version, Kohout, Berkman, Evans, & Cornoni-Huntley, 1993) of the Center for Epidemiological Studies Depression scale (CES-D; Comstock & Helsing, 1976; Radloff, 1977) is a standardized self-report questionnaire used to identify current symptoms of depression, with emphasis on depressed affect. The CES-D short form consists of 11 items (e.g., "I felt everything I did was an effort" and "I felt sad") rated on a 3-point Likert scale from "hardly ever or never=0" to "much or most of the time=2." Participants were asked to respond based on their feelings during the previous week. Total scores range from 0 to 22 with higher scores reflecting greater depressive symptoms. Unlike other measures of depressive symptoms (e.g., Beck Depression Inventory, Hamilton Rating Scale for Depression), the CES-D is relatively unaffected by physical symptoms and is, therefore, commonly used in research with medical patients (Devins et al., 1988). Coefficient alpha reliability in the present sample was .74, consistent with other research (Himmelfarb & Murell, 1983; Kohout et al., 1993).

Analytic approach

Correlations among the stress measures (objective stressors, event specific and global subjective measures) were examined to confirm convergent and discriminative validity. Pearson bivariate correlations were calculated among continuous variables and Spearman rank-order correlations were calculated when one variable was categorical and the other was continuous. Correlations were also used to test the significance and direction of association between the control variables, stress measures, and depressive symptoms. Next, hierarchical multiple regression (HMR) analyses along with squared semi-partials examined the explanatory power of the control variables and stress measures in relation to depressive symptomatology. Variables significantly correlated with depressive symptoms were tested in the regression analyses. Variable entry was determined by the a priori theoretical and empirical rationale specified above.

Results

Preliminary analyses

Descriptive data

Predictor variables. Descriptive data for the objective stressors is provided in Table 4. The majority (74%) of participants experienced at least one life event. The modal subjective stress associated with that event was 3.0=very much upsetting. The most common event reported was the death or serious illness of a relative or close friend. The mean of the IES-T was 25.3 (SD = 14.2, range 0-65), a value at least ½ SD higher than those reported in other breast cancer samples (M = 16.4, Cordova et al., 1995; M = 11.5, Baider, Peretz, & De-Nour, 1992). According to the scale authors, total scores above 19 are considered clinically significant in that feelings/behaviors are at a problematic level (Horowitz, Field, & Classen, 1993). Avoidance and Intrusion subscale means were 12.3 (SD = 7.9, range 0-36) and 12.9 (SD = 8.4, range 0-35), respectively. The average PSS-10 score was 18.6 (SD = 6.8, range 1-36), a value nearing 1 SD higher than the mean score from a national probability sample of adults (M = 13.02; Cohen and

Williamson, 1986). In summary, the data suggest that the participants were reporting significant psychological stress across both objective and subjective measures.

Outcome variable. CES-D scores ranged from 0 to 14 ($\underline{M}$ = 6.1; $\underline{SD}$ = 3.5). Based on previous psychometric studies of the CES-D (Andresen, Malgren, Carter, & Patrick, 1994), a cut-off score of $\geq$10 was considered suggestive of clinical depression. This score was also 1 SD above the sample mean. As can be seen in Figure 1, 19% ($\underline{n}$ = 32) of the participants had CES-D scores meeting/exceeding the cut-off. An additional 9% (n = 15) of the women had the score of 9, one point below the cut-off score. In all, one fifth of the women were experiencing depressive symptoms of possible clinical importance (i.e., $\geq$ 10). This is comparable to rates of depressive symptoms found in previous studies of women with breast cancer (Rijken, deKruif, Komproe, & Roussell, 1995; Watson et al., 1990).

Convergent and discriminative validity among the stress measures

Correlations between objective stressors and subjective stress measures are presented in Table 5 and demonstrate expected convergent and discriminant validity relationships. As would be predicted, number of events and perceived stress associated with those life events were correlated (17 of 21 correlations were significant ranging from .15 to .91). Importantly, there were zero or smaller correlations between these life events and the IES-T and its subscales (only 4 of 21 correlations were significant and they ranged from .13 to .21), suggesting that the objective life event measures and the subjective cancer stress measures were assessing differing aspects of stress. This pattern of correlations is also consistent with the findings of other research (e.g., Cohen et al., 1983; Pbert et al., 1992). In regards to the subjective cancer stress measure (IES), the data show that the subscales of the measure are correlated ($\underline{r}$ = .54), non-overlapping, and consistent with previous research reporting correlations of .51 (Epping-Jordan, Compas, &

Howell, 1994) and .68 (Cordova et al., 1995). The subjective measure of global stress (PSS-10) was related to most of the other stress measures (9 of 10 correlations were significant ranging from .13 to .51), though again, non-overlapping. Furthermore, correlations within measures (e.g., subscales of the IES) were higher than correlations between measures (e.g., IES and PSS-10). Finally, the magnitude of the correlations among the subjective stress measures was greater than those with objective stressors (e.g., Cohen et al., 1983).

Primary analyses

Correlations

Of the nine control variables tested (age, race, partner status, education, income, stage of disease, type of surgery, DSS, and neuroticism), only two were significantly correlated with depressive symptoms, race ($r = -.19$, $p < .01$) and neuroticism ($r = .38$, $p < .0001$). Thus, both being of minority status (i.e., African American or Hispanic) and having higher levels of neuroticism were related to higher CES-D scores. Based on these results, race and neuroticism were included in the regression analyses.

Correlations among objective stressors, subjective stress measures, and depressive symptoms are presented in Table 6. The total number of life events and life event stress, while significantly correlated with depressive symptoms, were not included in further analyses due to multicollinearity with absence/presence of objective stressors.[2] As "major financial difficulty" and "major conflict with children or grandchildren" were the life events significantly ($p < .05$) correlated with CES-D scores, they were also included. As expected, the subjective measures (life event stress, IES-T and its subscales, and PSS-10) were significantly correlated with CES-D scores ($p < .01$). As the shared variance between the PSS-10 and the CES-D was noteworthy ($r = .63$; 40%), we wished to rule out the possiblity of measure overlap at the item level. Results of a factor analysis verified no overlap of items between measures.[3] Thus, the results described below are not confounded by shared item/content variance between the PSS-10 and CES-D.

Regression

HMR was used to examine the relative power of objective stressors, event specific subjective stress, and subjective global stress in predicting depressive symptoms after controlling for the effects of race and neuroticism. The a priori entry was as follows: Step 1) race, 2) neuroticism, 3) objective stressors (major conflict with children or grandchildren and major financial difficulty), 4) IES-T, and 5) PSS-10.

Table 7 provides the results of the HMR, emphasizing the change in variance in depressive symptoms accounted for when the control variables (race and neuroticism) and the predictors (major financial difficulty, major conflict with children or grandchildren, IES-T, and PSS-10) were added to the model. With HMR, 51% (total adjusted $R^2 = .496$) of the variance in depressive symptoms was accounted for by the full model. Of note, global stress remained a significant predictor of depressive symptoms after accounting for the effect of all the other variables in the regression.

Table 8 shows results for the final regression model, equivalent to the full model represented by Step 5 in Table 7. In this model, squared semi-partial correlations, sr^2, indicate the amount of variance accounted for by a given variable above and beyond all other variables in the regression model (Cohen & Cohen, 1983). Therefore, based on the sr^2 for the final regression model, which indicates the amount of variance accounted for by each variable had it been last in the regression equation, the best predictor of depressive symptoms was global stress (10%), followed closely by cancer stress (8%). Race, the remaining significant variable in the final regression model, added little unique variance (approximately 1%) in predicting depressive symptoms.

While neuroticism and the objective stressors (major financial difficulty and major conflict with children or grandchildren), introduced at Steps 2 and 3 respectively, added significant amounts of variance in the HMR, neither were significant predictors of depressive symptoms in the final regression model. Neuroticism may not have been signficant due to global stress mediating its influence or to multicollinearity (neuroticism was most highly correlated with global stress, $r = .45$, $p < .0001$, as opposed to any other variable in the study). However, the objective stressors did approach significance ($p = .057$). In examining the squared semi-partials (sr^2) for these variables, the unique variance accounted for in depressive symptoms is mostly attributable to the contribution of major financial difficulty (approximately 1%) rather than to that of major conflict with children or grandchildren (0%).

Follow-up analyses

Because of the empirical and clinical importance of the cancer stress measure, we wished to test the relative contribution of avoidance versus intrusive thoughts/behaviors to depressive symptoms. Therefore, a second regression was conducted using the IES subscales, IES-A and IES-I, in place of the IES-T. Variables were entered as before: Step 1) race, 2) neuroticism, 3) major conflict with children or grandchildren and major financial difficulty, 4) IES-A, 5) IES-I, and 6) PSS-10. IES-A was entered before IES-I because of its weaker relationship with psychological outcomes. Results from this follow-up indicate that, 52% (total adjusted $R^2 = .500$) of the variance in depressive symptoms was accounted for by the HMR, $F(7, 158) = 24.54$, $p < .0001$. Specifically, the IES-A did not contribute a significant increment of unique variance to the final model (beta = .089, $t(160) = 1.31$; $sr^2 = .005$). This finding is consistent with previous literature (e.g., Baider & De-Nour, 1997; Cordova et al., 1995), zero or weak relationships between avoidant thoughts/behaviors and psychological distress. However, both intrusive thoughts/behaviors (IES-I) and global stress (PSS-10) were predictive of depressive symptoms in the final regression model (IES-I: beta = .291, $t(159) = 4.01$, $p < .0001$ and PSS-10: beta = .379, $t(158) = 5.32$, $p < .0001$) accounting for 5% ($sr^2 = .049$) and 9% ($sr^2 = .086$) of the variance, respectively. Again, global stress was the best predictor of depressive symptoms.

Discussion

The present study examined the relative explanatory power of objective stressors (life events) and subjective stress measures (event specific, global) in relationship to depressive symptoms. This examination occurred in the context of an important, naturally occurring event, the diagnosis and treatment of cancer. Our hypotheses were confirmed: 1) subjective measures of stress were better predictors of depressive symptoms than an objective measure (life events); and 2) a measure of one's global perceptions of stress was a better predictor of depressive symptoms than a measure of perceived stress for the specific event (i.e., cancer).

These findings are consistent with others (e.g., Cohen et al., 1983) and underscore the importance of perceptions or appraisals of stress (instead of or in addition to the assessment of events, per se) when examining the relationship between stress and psychological outcomes. Indeed, a global perception of stress, as assessed with the PSS-10, was the strongest predictor of depressive symptoms. While the difference between the contribution of the PSS-10 and the event specific subjective measure (IES) was small (10% vs. 8%, respectively), this finding remains impressive considering the clinical importance of the event -- cancer diagnosis and treatment. Interestingly, many women in the study have told us that they were approached for study participation on "the worst days of my life." Relatedly, one of the most common reasons for refusing participation was the report of feeling "too stressed" to participate. Furthermore, when the mean values on the PSS-10 and IES were compared with data from other cancer or normative samples, the present values were, at a minimum, one-half to one standard deviation higher. This provides empirical support for the fact that many of the women were stressed not only by their cancer experience but with life, in general, as well.

In comparison to the perceptions of global stress and stress specific with the cancer "event," the contribution of other recent, difficult, and upsetting events -- such as death or serious illness of a close friend or relative or major financial difficulty-- to the prediction of depressive symptoms was minimal. The contribution of these other stressful events may be smaller because their impact may have lessened with time. For instance, these events occurred at some point in the past 12 months, and they may have resolved by the time of assessment. Meanwhile, the time from cancer diagnosis to post surgery recovery and study participation was, on average, a matter of 4 weeks. The confounding of the rating interval with the measure (e.g., past 12 months for the objective stressors vs. past month for global stress and past week for cancer specific stress) has a statistical effect on the magnitude of the correlation between the measures and the outcome. In this case, the relationship between the subjective stress measures and the outcome would be expected to be higher because of the shorter and more proximal rating interval. Another methodological difference between the measures is the item format. That is, measures assessing the degree of distress associated with life events typically use only one item per event, which reduces the reliability of the measure. This contrasts with the multiple item format of a measure like the IES. Taken together, these methodologic aspects of objective stress measures may contribute to the findings reported here, as well as others, which suggest that event measures are, on average, weaker predictors in comparison to subjective global stress measures (Cohen et al., 1983; Martin et al., 1995; Pbert et al., 1992), even when some of the objective events rated are the most difficult ones individual's can experience (e.g., death of a loved one).

Finally, in testing the relationship between stress and depressive symptoms, we controlled for variables such as sociodemographics (age, race, partner status, education, and income) and personality (neuroticism), all of which are known to covary with stress or the perception of stress. While important for study in their own right, these variables were controlled here because they were not the focus of study. In addition to personality and sociodemographic variables, we also chose ones relevant for the present paradigm--disease characteristics (e..g, stage of disease, surgery type, days since surgery). Of all the control variables, only a sociodemographic one, minority status, was significantly related to depressive symptoms in the final model of the HMR. This finding does not reflect an SES difference in the sample, as we separately tested and found no significant differences in family income, years of education, and partner status. It is possible that this finding is related to other variables associated with race/ethnicity and cancer outcomes such as knowledge and attitudes and/or access to adequate care (see Meyerowitz, Richardson, Hudson, & Leedham, 1998, for a review). As the number of minority participants in the present study was small ($\underline{n}$ = 16, 10% of the total sample), the latter finding will require replication before a general conclusion can be made. In any case, the inclusion of the control variables provided data to rule out alternative, plausible hypotheses for our findings.

Clinical implications of the findings

In addition to the methodologic focus of this study, the findings also provide an important look at the emotional crisis that surrounds cancer diagnosis and surgery. Our earlier research on the emotional responses to cancer diagnosis (Andersen et al., 1989) found that depressive and confused moods were unique emotional responses. While anxious reactions were common as well, they are likely part of the general emotional response to a medical diagnosis and the anticipation of medical treatment, rather than cancer, per se. More recently, we have reported that cancer specific stress (as indexed by the IES) is not only emotionally upsetting, but is related to a negative biologic response -- immune down regulation (Andersen et al., 1998), and we have hypothesized that such a scenario may adversely impact the course of the disease (Andersen et al., 1994). These data indicate that the stress indexed by the IES, coupled with the global feelings of stress and recent life event stressors, may conspire to heighten one's risk for depressive symptomatology. In reviewing the literature on psychosocial interventions (Andersen, 1992), we noted that stress reduction is a component of successful interventions. Considering these data along with our other studies, they suggest that stress reduction should be included to not only lower stress and anxiety, but to possibly reduce other negative affective symptoms (e.g., depressive ones) which can also have important biologic effects (Herbert & Cohen, 1993).

In considering other specific findings and their clinical importance, while a majority of women reported experiencing the death or serious illness of a close friend or relative in the previous 12 months (a fact not surprising considering the age range of the sample), it was "major financial difficulty" and "major conflict with children or grandchilden" that were significantly correlated with depressive symptoms ($\underline{p}$ < of .01 and .05, respectively), and these events approached significance in the HMR ($\underline{p} < .057$) as predictors of depressive symptoms. While we do not know if these life events represented chronic circumstances or new stressors, research has indicated that the cancer experience can have detrimental consequences on both finances (e.g., loss of income due to work absences, increased insurance costs; McKenna, 1991; McKenna & Toghia, 1989) and family relationships (e.g., increased tension between partners with young children in the home, Vess, Moreland, & Schwebel, 1985; decreased availability of support due to increased family/partner strain/distress, Baider & De-Nour, 1988; Cassileth et al., 1985; see Sales, Schulz, & Biegel, 1992, for a review). As 28% of all households are headed by unmarried women and 57% of all women work outside the home (U.S. Bureau of the Census, 1995; 1996), these two stressors, in particular, may be important to the psychological functioning of women with breast cancer.

One can easily forsee how financial and/or family problems could effect multiple aspects of the cancer experience. For instance, these stressors may be involved in the selection of medical therapies (e.g., insurance coverage of chemotherapy vs. bone marrow transplantation) and/or delay of medical treatment (work and/or child care conflicts), create transportation difficulties (multiple family obligations), impair the quality/availability of support (e.g, increased tension in the home) , and decrease, overall, quality of life. Therefore, the data suggest that these stressors (whether new or old) and their potential negative impact on the already stressful experience of a cancer diagnosis may increase one's vulnerability to depressive symptoms, affect treatment compliance, and possibly longterm survival as well (especially if women are not receiving recommended medical treatment; e.g., Bonadonna & Valagussa, 1981; Coates et al., 1992). Health care providers may want to be particularly aware of those women who are struggling financially and/or experiencing interpersonal conflicts. Linking women with appropriate psychological, social, and/or financial services would be important. In particular, the benefits of psychological interventions (e.g., improved coping, better communication, increased mood) for people with cancer have been well-documented (Andersen, 1992).

In conclusion, these data demonstrate the value of assessing both objective stressors and subjective stress (event specific and global). Such information can increase our understanding of how life events and stress perceptions are related to psychological functioning as well as identify circumstances in which people may be in need of intervention. Given the design of the current study, no causal inferences can be made. However, future research can examine the reliability of these relationships longitudinally, establish causal explanations, and test their generalizability with other cancer groups.

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Footnotes

[1]Data from the first 116 women accrued to the Stress and Immunity Breast Cancer Project (including 116 of the 166 women included here) have appeared in a report of the negative relationship between stress (as indexed by the IES) and multiple immune indicators (Andersen et al., 1998). Aside from the IES, there is no overlap of measures between Andersen et al. (1998) and the present report.

[2]The correlation between the total number of life events and life event stress was $r = .91$ ($p < .0001$), indicating shared variance. Including both of the variables in the regression equation would have been redundant. Of additional concern was the collinearity between the objective stressors and the perceived stress associated with them. Collinearity was likely due to the strategy of assessing life event stress with one item using a 3-point scale, which did not allow for sufficient variance among participants. We tested this variance using oneway ANOVAS with CES-D as the dependent variable and the 3 life event distress categories (not much, some, very much) as the independent variable for all 5 of the life events assessed. None of the ANOVAS were significant at $p < .05$, all F's ≤ 2.7. Thus, experiencing a life event was akin to being distressed by that event. As all women did not experience a life event, there was greater variation between those women who did not experience a life event versus those women who did experience one or more life events. As such, it was decided to enter only those objective stressors significantly correlated with CES-D scores in the regression equation.

[3]We conducted a PACE factor analysis using the program CEFA (Browne, Cudeck, Tateneni, & Mels, 1998). According to previous research, the short form of the CES-D has 4 factors (1-depressed affect; 2-postitive affect; 3-somatic complaints, and 4-interpersonal problems; Kohout et al., 1993) while the PSS-10 has 2 identified factors (1-distress; 2-coping;

Cohen & Williamson, 1986; Hewitt et al., 1992; Martin et al., 1995). We combined the PSS-10 and CES-D, and oblique rotation to a partially specified target (Browne, 1972) was carried out to test the factor loadings for construct redundancy. Loadings anticipated to be zero were minimized in the rotation process and values of the remaining loadings were left unspecified. Thus a pattern suggested by current research (6 factors) was tested and a rotation to a solution as close to the target as possible was carried out. As an additional check, we also conducted factor analyses for 4, 5, and 7 factors.

The RMSEAs, measuring goodness of fit, for the factor solutions were as follows: 4 factors = .072, 5 factors = .067, 6 factors = .058, and 7 factors = .060. The RMSEA values for the 4 and 5 factor solutions were unsatisfactory (scores ≤ .05-.06 are judged acceptable). While the RMSEA values for the 6 and 7 factor solutions were both acceptable, the 7 factor solution showed evidence of overfactoring as indicated by the direct quartamin rotation in which there were two moderate loadings on the seventh factor and the other factor loadings were low, negative values (approximating zero). Therefore, the variance accounted for by the seventh factor was uninterpretable. The 6 factor solution, however, demonstrated high loadings that corresponded to the target and reflected previous findings. Additionally, the confidence intervals corresponding to the target zero loadings generally overlapped with zero and the residuals appeared satisfactory since they did not demonstrate a pattern among the items. These results were not only consistent with previous research but, in fact, indicated no item overlap among the two measures in the present sample.

Table 1

Types of Stress Measures

Objective (stressors)	
	- Type of Life Event (e.g., finanical loss, bereavement, job loss)
	- Total Number of Life Events
Subjective (perceived stress)	
	- Event Specific (stress associated with identified event)
	- Global (stress associated with life in general)

Table 2

Sociodemographic and Disease Characteristics of Sample

		Sociodemographics n (%)
Age (years):		M(SD) = 50(11)
Race:	White	150 (90)
	Minority	16 (10)
	African American	14 (9)
	Hispanic	2 (1)
Living with spouse/partner:	Yes	119 (72)
	No	47 (28)
Education (years):	<12 years	4 (2)
	12 years	37 (22)
	13-15 years	48 (29)
	16 years	30 (18)
	>16 years	47 (28)
Annual family income:	<$15,000	14 (9)
	$15-29,000	28 (18)
	$30-49,000	35 (22)
	$50-79,000	35 (22)
	≥$80,000	44 (28)

	Disease characteristics
Stage: II	142 (86)
III	24 (14)
Surgery type: Lumpectomy	65 (39)
Mastectomy	101 (61)
Modified Radical	95 (57)
Radical	1 (1)
Elective Bilateral	5 (3)
Days since surgery (DSS):	M(SD) = 36(16.6)

Note. N = 166. Disease staging was based on the American Joint Committee on Cancer and the International Union Against Cancer staging systems. Days since surgery were calculated as the number of days between surgery and the initial assessment.

Table 3

Stress Measures Used

Objective (Stressors)	
- Type of Life Events	
	1) Death or serious illness of a close friend or relative
	2) Major financial difficulty
	3) Divorce or other breakup involving family members (spouse) or close friends
	4) Major conflict with children or grandchildren
	5) Muggings, robberies, accidents, or similar events
- Total Number of Life Events	
Subjective (Perceived Stress)	
- Event Specific	
	1) Life Event Stress (Stress associated with life events)
	2) Cancer Stress (Impact of Events Scale-IES)
- Global	
	1) Perceived Stress Scale (PSS-10)

Table 4

Number and Type of Life Events

Number of events reported	n (%)
0	44 (26)
1	70 (42)
2	26 (16)
3	18 (11)
4	7 (7)
5	1 (1)

Type of events reported	n (%)
Death or serious illness of close friend or relative	79 (38)
Major financial difficulty	45 (22)
Major conflict with children or grandchildren	30 (14)
Divorce or breakup involving family members/close friends	29 (14)
Muggings, robberies, accidents or similar events	25 (12)

Note. N = 166.

Table 5

Correlations among Objective Stressors (Life Events) and the Subjective Stress Measures

Measure	1	2	3	4	5	6	7	8	9	10	11
1. Death/Illness	1.00										
2. Finances	.08	1.00									
3. Conflict	-.01	.21**	1.00								
4. Crime/Accident	-.03	.20**	.20**	1.00							
5. Divorce/Breakup	.13*	.22**	.16*	.12	1.00						
6. # Events	.49****	.62****	.53****	.50****	.57****	1.00					
7. Event stress	.40****	.54****	.49****	.53****	.47****	.91****	1.00				
8. IES Total	.09	.09	.07	.05	.05	.13*	.13	1.00			
9. IES-A	.14*	.13*	.13*	.06	.10	.21**	.19**	.87****	1.00		
10. IES-I	.02	.08	-.01	.04	.00	.03	.04	.89****	.54****	1.00	
11. PSS-10	.02	.19**	.20**	.12	.14*	.24***	.29****	.51****	.51****	.38****	1.00

Note. 1. Death/Illness = Death or serious illness of a friend or close relative; 2. Finances = Major financial difficulty; 3. Conflict = Major conflict with children or grandchildren; 4. Crime/Accident = Muggings, robberies, accidents, or similar events; 5. Divorce/Breakup = Divorce or breakup involving family members or close friends; 6. # Events = Total number of life events.

$^{*}p \le .05$. $^{**}p \le .01$. $^{***}p \le .001$. $^{****}p \le .0001$.

Table 6

Correlations among Objective Stressors, Subjective Stress, and Depressive Symptoms

	CES-D	
Stress Measure	r	p
Objective (Stressors)		
Death or serious illness of close friend or relative	-.00	.49
Major financial difficulty	.18	.01
Divorce/breakup involving family members/close friends	.04	.31
Major conflict with children or grandchildren	.13	.05
Muggings, robberies, accidents, or similar event	.01	.46
Total number of life events	.16	.02
Subjective (Perceived Stress)		
Life Event Stress	.17	.01
Cancer Stress (IES-T)	.58	.0001
IES-A	.44	.0001
IES-I	.56	.0001
Global Stress (PSS-10)	.63	.0001

Table 7

Hierarchical Regression Results for the Prediction of Depressive Symptoms

Step	ΔR^2	$F(\Delta R^2)$	TR^2	$F(TR^2)$
1. Race	.035	5.89*	.035	5.89*
2. Neuroticism	.142	28.06**	.176	17.46**
3. Debt/Conflict	.022	2.20	.198	9.96**
4. IES-T	.216	59.13**	.415	22.67**
5. PSS-10	.099	32.47**	.514	28.02**

Note. $N = 165$. Abbreviations include: ΔR^2 = Change in squared multiple correlation; $F(\Delta R^2)$ = Value and significance of change in squared multiple correlation; TR^2 = Squared multiple correlation for total equation; $F(TR^2)$ = Value and significance of sqared multiple correlation for total equation. Debt = major financial difficulty and Conflict = major conflict with children or grandchildren.

* $p < .01$. ** $p < .0001$.

Table 8

Results of Final Regression Model for the Prediction of Depressive Symptoms

Independent variable	Beta	t	sr^2
Race	-.108	-1.918*	.012
Neuroticism	.081	1.283	.005
Debt	.092	1.590	.008
Conflict	.006	.099	.000
IES-T	.330	5.097**	.079
PSS-10	.398	5.698**	.100

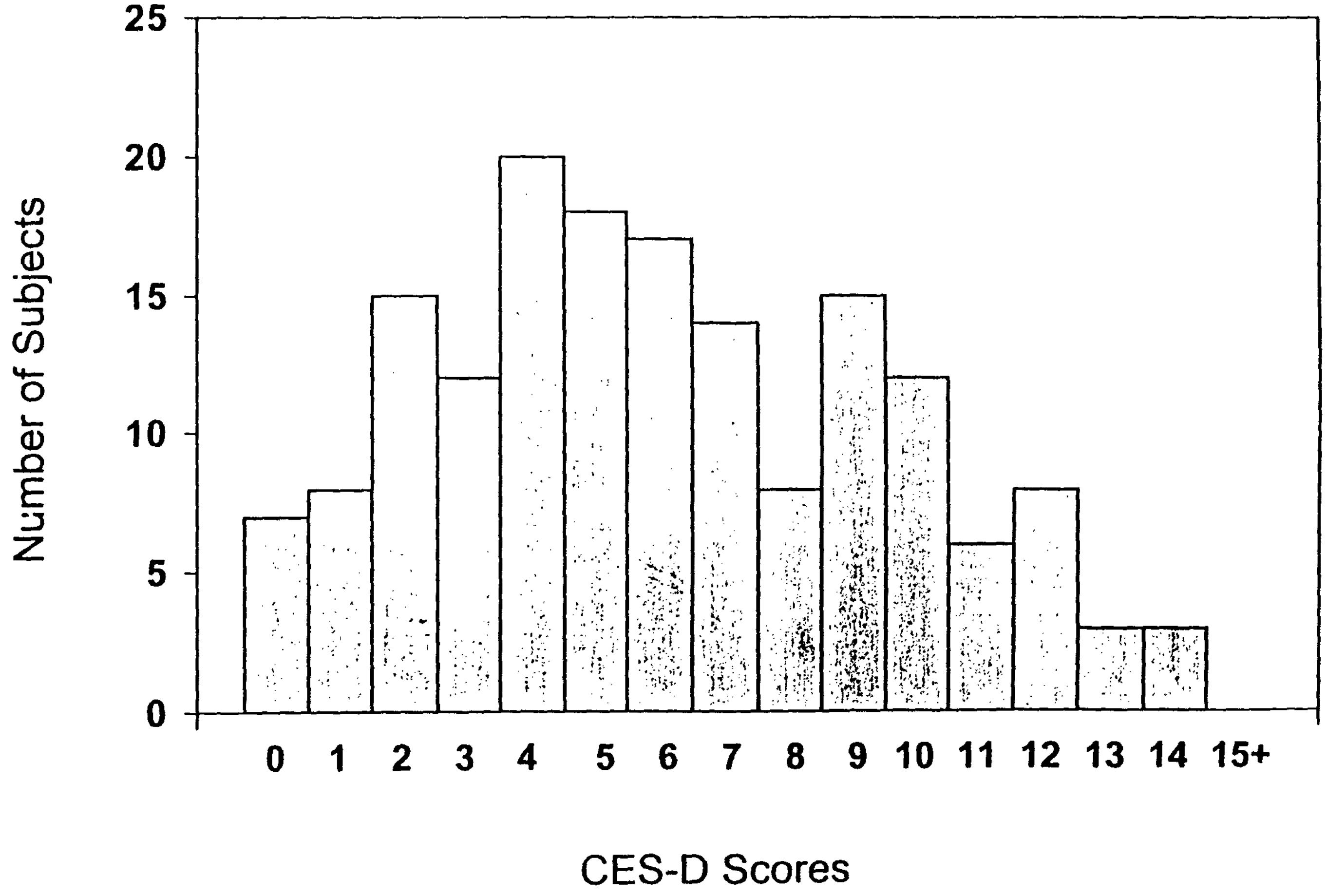
Note. N = 165. Abbreviations include: Debt = major financial difficulty and Conflict = major conflict with children or grandchildren.

* $p < .05$. ** $p < .0001$.

Figure Caption

Figure 1. Distribution of CES-D scores.

Figure 1


25
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Number of Subjects
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15+
CES-D Scores

- Unpublished Data -
Under review

Recovery of Tumor Antigen (MUC1) Specific Antibody Following Successful Stress Reduction in Breast Cancer Patients Randomized to a Psychological Intervention in Addition to Standard Therapy

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ABSTRACT

Stress with breast cancer diagnosis and treatment negatively influences immune responses. We hypothesized that stress reduction might positively influence an anti-tumor immune response against a breast cancer antigen MUC1. Women surgically treated for regional breast cancer were randomized to psychological/behavioral intervention or assessment only study arms. Women receiving the intervention showed a significant lowering of stress as indexed by serum cortisol, fewer depressive symptoms, and prompt recovery and maintenance of anti-MUC1 antibody response. Assessment only women had higher cortisol, more depressive symptoms, and permanently lost anti-MUC1 antibody responses. These are the first experimental data showing a convergence of psychological, endocrine, and immune effects with a psychological/behavioral intervention, and, importantly, the intervention enhanced a breast cancer relevant immune response.

INTRODUCTION

A diagnosis of cancer and cancer treatments are objective, negative events in an individual's life. Although negative events do not always produce stress and a lowered quality of life, data from many studies document severe, acute stress at diagnosis[1] and the potential for continuing stress[2]. Stress and deterioration in quality of life are important targets for cancer control efforts[3,4] in that they co-occur with adverse biologic consequences.

The body's response to stress involves the autonomic, endocrine, and immune systems. Psychological stress is associated with the activation of the hypothalamic-pituitary-adrenal (HPA) axis, and cortisol, the main hormone to reflect adaptation to stress, is produced[5-7]. Psychological distress and stressors (i.e. negative life events) are also associated with immune system changes, primarily down-regulation[8,9].

In addition to each system being singly responsive to stress, the neuroendocrine and the immune systems provide an integrated mechanism necessary for maintenance of the body's proper defense function. For example, leukocytes are key effectors and provide an important representation of the state of activation for the immune system. Leukocytes can also make cytokines that, in turn, are available to regulate the production of hormones by the neuroendocrine system. Lymphocytes, on the other hand, have receptors for neuroendocrine peptides and hormones and have the ability to produce each as well. In sum, stress can produce perturbations in both the endocrine and the immune systems.

There is accumulating evidence that stress and its biologic consequences occur in the context of cancer. Our previous studies with women with breast cancer who were assessed during the post surgery recovery period found that high levels of stress were related to the down regulation of a panel of cellular immune responses, including NK cell function (i.e. lytic activity, response to rIFN-γ) and T cell function (i.e., proliferation and blastogenesis)[10]. Levy[11] also reported on stress and immunity in women with breast cancer and found that estrogen receptor status predicted NK cell lysis, and social support, a variable hypothesized to reduce stress, was correlated with higher NK cell activity. Together, these findings suggest that if an individual with cancer is significantly stressed, and nothing is done to alleviate it, then stress may negatively influence his/her immune response.

Psychological intervention studies with cancer patients can produce impressive reductions in stress and improvements in quality of life. This is particularly true for breast cancer patients and patients at greatest risk for psychological/behavioral morbidity, such as those with more extensive disease[12]. However, few studies have measured endocrine and/or immune responses, instead relying on psychological or behavioral measures. An exception to this is a study by Fawzy et al.[13,14], who conducted a randomized investigation to reduce stress for newly diagnosed and surgically treated melanoma patients. They reported lower levels of mood disturbance and enhanced immune function (e.g. NK cell lysis) for the intervention group.

Psychological interventions designed for stressed but otherwise healthy individuals have yielded significant reductions in serum cortisol with concomitant improvements in the individuals' moods[15-19], yet unfortunately, immune measures were not included in these studies. Research focusing on the relationship between stress and immunity in humans has not included endocrine measures, and the immune measures were usually non specific (e.g. quantitative measures of cell number, functional measures of blastogenesis or lysis)[8,9], with few exceptions[20,21]. The study we report here used an experimental design that included psychological, endocrine, and immune measures, and, importantly, monitored a specific immune response against a breast tumor antigen, MUC1.

Patients with breast cancer develop humoral as well as cellular immune responses to several breast cancer related molecules, such as HER-2/neu, p53, and MUC1[22]. In general, the presence of an immune response against the tumor is correlated with a more favorable prognosis. Unlike the other antigens that are each expressed only in a subset of breast cancers, MUC1 is expressed by all breast cancers, primary tumors as well as metastases[23]. Varying but detectable levels of anti-MUC1 antibodies can be found in all patients. Furthermore, it has been shown that elevated levels of anti-MUC1 antibody and/or immune complexes present in patients' serum at the time of diagnosis strongly protect against disease progression and correlate with an increase in disease free interval and overall survival[24]. Furthermore, the presence of a humoral response is suggestive of activation of other immune mechanisms, and so assessment of anti-MUC1 antibody served as a surrogate marker of an overall anti-tumor response in the patient. It has been shown, for example, that in addition to the humoral response, breast cancer patients generate weak but measurable cytotoxic T cell responses that have also been correlated with good prognosis[25,26].

Our intent was to experimentally determine if an intervention designed to reduce cancer related stress and enhance mood could also influence biologic responses, that is, to down regulate endocrine stress responses and up-regulate immune responses. Our biobehavioral model of cancer stress and disease course[27] suggests that enhanced biologic responses may accrue from stress reduction and improvements in quality of life resulting from psychological interventions. We selected women who had been diagnosed and surgically treated for regional breast cancer. Prior to beginning standard adjuvant therapy, all patients completed a questionnaire assessing symptoms of depression and provided a serum sample for assaying levels of cortisol and anti MUC1 antibody response. Women were randomized to one of two arms: Intervention and assessment or Assessment only. The 12 month psychological/behavioral intervention, designed to reduce stress and improve quality of life, consisted of an intensive phase with weekly sessions for 4 months and then a maintenance phase with monthly sessions for 8 months. Monitoring of all patients was repeated at 4, 8, and 12 months. Thus, the pretreatment assessment of anti-MUC-1 antibody and its recovery and maintenance post adjuvant cancer therapy provided a disease specific marker (and an overall marker of anti-tumor response) against which we assessed the immunologic consequence of a psychological/behavioral intervention. Additionally, the data provided the opportunity to examine psychological and endocrine mechanisms for an anti MUC1 antibody response.

RESULTS

Equivalence of study arms at pretreatment

Analyses were conducted to rule out the presence of pretreatment group differences on variables which could potentially be confounded with outcome, including sociodemographic variables, aspects of disease/treatment, and health behavior correlates of stress. One way analysis of variance (ANOVA) comparisons (i.e. Group: Intervention vs. Assessment only) for the sociodemographic variables revealed no significant differences between groups on the variables of race, age, marital status, presence of a significant other (e.g. spouse), education, employment status, or annual personal income ($p > .05$).

Randomization also resulted in the groups being equivalent in important disease and treatment related variables. ANOVA's comparing groups revealed that the study arms were equivalent (p's > .05) on the variables of stage, tumor size, numbers of positive nodes, ER status, menopausal status, surgery type, incidence of radiation treatment, days since surgery, and Karnofsky Performance status at accrual. Perhaps even more important in view of the immune focus of the study, dose intensity was calculated for each of the chemotherapy drugs prescribed to each patient at the time of accrual. The agents were Cytoxan, Adriamycin, 5-FU, Methotrexate, and/or Taxol. ANOVA's indicated that the two study arms were recommended to receive equivalent doses of all chemotherapy drugs (adjusted for patient's body surface area), with the exception of the recommended dose for Adriamycin [$F(2, 73) = 5.80$, $p < .01$]. The Intervention group was recommended to receive a significantly higher dose ($M = 40.02$) of Adriamycin than the Assessment only group ($M = 35.17$). As this group difference in favor of the Assessment only arm went against the hypotheses for the study (i.e., we predicted that the Intervention group would have improved psychological, endocrine, and immune outcomes regardless of the magnitude of the standard therapy), the analyses did not control for this difference.

As the psychological outcome was depressive symptoms, we also tested for initial group differences on variables that are often correlated with acute stress or depressive symptoms, such as negative health behaviors (i.e. history of alcoholism/current alcohol use, current smoking), low rates of positive health behaviors (e.g. high fat/low fiber intake, low rates of exercise), or vegetative signs of depression (e.g. weight loss, sleep problems). One-way group comparison ANOVA's for these variables were not significant (p's > .05). Taken together, these preliminary analyses indicated that the randomization procedure was effective in establishing equivalence between the study arms for sociodemographic, disease and treatment, and other variables which could covary with psychologic or biologic outcomes.

Effects of the intervention on stress reduction

A repeated-measures ANOVA was calculated to test the hypothesis that cortisol levels for women in the intervention group would decline following the intensive intervention, as compared to levels for women in the assessment only group. The Group x Time [$F(3, 73) = 3.02$, $p < .05$] interaction was significant, but the Group x Time x Stage interaction was not significant. More specifically, within-subjects contrasts indicated that mean cortisol levels in the Intervention group decreased significantly following the period of intensive intervention as compared to the cortisol levels for the Assessment only group. In fact, an examination of Figure 1 indicates that mean cortisol levels for Assessment-only women actually rose from the initial assessment to the four-month assessment, while Intervention group means declined during the same period.

A repeated-measures ANOVA was calculated to test the hypothesis that depressive symptoms (CES-D) would decrease for women in the Intervention arm following the intensive weekly intervention (i.e. from initial to 4 months), as compared the level of depressive symptoms for the patients randomized to Assessment only. Whereas there were no significant Group x Time interaction effects, the Group x Time x Stage interaction was significant [$F(3,83) = 2.79$, $p < .05$]. Within-subjects contrasts comparing the change in depressive symptoms from the initial assessment to the follow up assessments showed no significant differences. However, an examination of the CES-D means indicates that the depressive symptoms for Stage III women in the Intervention arm declined from the initial to the four month follow up, while the depressive symptoms for the Stage III patients in the Assessment only arm actually rose during the same period. There were no significant changes over time in CES-D means for Stage II patients.

Effects of the intervention on MUC1 specific antibody responses

For each of three serum dilutions, 1:20, 1:40, and 1:80, a repeated-measures ANOVA was calculated in order to test the hypothesis that anti MUC-1 antibody levels for women in the Intervention arm would recover following the intervention (i.e. 8 or 12 months), as compared to levels for the women in the Assessment-only arm. For the 1:20 and 1:40 dilutions, both the Group x Time and the Group x Time x Stage interactions were significant, and approached significance for the 1:80 dilution (see Table 1).

Within-subjects contrasts and examinations of group means showed a similar pattern of anti MUC-1 antibody response over time for 1:20, 1:40, and 1:80 dilutions, as indicated in the three panels for Figure 2. Prior to randomization, women in both groups yielded similar anti MUC-1 antibody responses. At four months, when standard chemotherapy treatment was being received by the majority (85%) of the sample, antibody levels declined in both study arms. It is known that chemotherapy affects both B cells that secrete the antibody as well as helper T cells which help B cell antibody production. The number of women receiving chemotherapy declined by the 8 month (22% of the entire sample) and 12 month (4% of the entire sample) assessments, and so it would be expected that there would be some leveling off at 8 or 12 months of the antibody response decline observed at 4 months. Indeed, the latter scenario was observed for the patients in the Assessment only arm. In contrast, the patients in the Intervention arm promptly recovered anti-MUC1 antibody responses. As predicted, within-subjects contrasts showed that MUC-1 levels for patients in the Intervention arm significantly rebounded by the 8-month and 12-month assessments than was the case for patients in the Assessment only arm. Specifically, MUC-1 levels remained significantly lower for the Assessment only arm than for the Intervention arm at 8 months for the 1:20 dilution [$F(1,77) = 4.29$, $p < .05$] and at 12-months for the 1:20 dilution [$F(1,77) = 4.14$, $p < .05$] and the 1:40 dilution [$F(1,77) = 3.96$, $p < .05$]. For the 1:40 dilution, the within-subjects contrast at 8 months approached significance [$F(1,77) = 3.59$, $p = .06$].

Regarding the Group x Time x Stage effects, at eight months, this effect was significantly stronger in Stage III patients for the 1:40 dilution [$F(1,77) = 3.99$, $p < .05$]; these data for Stage II and Stage III patients are displayed in the two panels in Figure 3. The remaining Group x Time x Stage contrasts were not significant.

The majority of the anti-MUC1 antibody response in breast cancer patients is of the IgM isotype which reflects the tandemly repeated nature of B cell epitopes along the MUC1 polypeptide core[28]. Some patients, however, also develop low level IgG responses. We performed isotype specific ELISA on the subset of serum samples to test for the possibility that recovery of antibody responses may also have been accompanied by isotype switching and presence of new isotypes. We found that this was not the case. The antibody isotypes present at the 8 and 12 month assessments were the same as those found pretreatment (data not shown).

DISCUSSION

> In breast cancer "a paradoxical situation exists: Optimism results from emerging insights into the basic genetic and biochemical mechanisms of breast cancer. Frustration grows from the poor record of the past in terms of extending life and improving the quality of life" (Institute of Medicine, National Academy of Science[3]; pg. 1).

The psychosocial burdens of cancer are notable in number, severity, and scope (see 29-31 for reviews), and finding strategies to reduce stress and prevent deterioration in quality of life (QoL) has become an important national research objective in cancer control[4]. Our data show that a psychological/behavioral intervention can result in reductions in important symptoms--depressed affect and stress, as indexed by cortisol lowering. While improvements in psychological outcomes for cancer patients have been demonstrated (see 12 or 32 for reviews), concurrent documentation by reduction of an HPA axis response has not been shown. Changes in the behavioral and psychological aspects of stress and depression are important, as recent data suggest that stress and depressive symptoms are among the ones that lead women with breast cancer to seek out psychological therapies and stress reduction techniques (e.g. relaxation) for assistance in coping during the first year following diagnosis[33].

That the intensive (weekly) phase of the intervention was associated with a lowering of a HPA axis stress response is an important finding. While the design of this experiment can not identify what component of the intervention led to the lowering of cortisol, per se, it is likely that training the patients in the use of progressive muscle relaxation as a behavioral coping strategy was important to reduce feelings of bodily tension and stress and/or cope with unpleasant treatment side effects (e.g. fatigue, sleep difficulties, nausea, vomiting, pain). In fact, we examined the correlation between the initial cortisol values and the womens' reports of their weekly frequency of relaxation practice, and the correlation was .39, indicating that women with initially higher cortisol levels also reported more regular use of relaxation training. This particular method, a specified sequence of tension-release cycles for large muscle groups of the body paired with instructions to focus on the bodily sensations of relaxation[34], was selected because of its differential effectiveness in producing positive psychological and physiologic effects (e.g. reductions in heart rate, respiration or EMG assessed muscle tension) in other groups with health difficulties. For example, the use of biofeedback assisted relaxation training with other patient groups (e.g., muscle tension feedback with Type II diabetics[35] or persons with essential hypertension[17]) has resulted in significant decreases in urinary/plasma cortisol, and such decreases have been sustained for as long as one year following training[18]. Conversely, when cortisol remains elevated it has been associated with adverse health conditions (e.g., atherosclerosis[36], cognitive deficits[37]) in both stressed and non stressed adults.

To our knowledge, these are the first experimental data to demonstrate a connection between an endocrine and a disease specific immune response in the context of a psychological intervention for cancer patients. Our results show that the ability to activate immune memory cells and/or prime naïve cells is present in the context of intervention, but much lower or absent in the assessment only group. What best correlates with this ability are levels of cortisol measured in the two groups. The Assessment only group maintained initially high levels of this stress hormone and appeared unable to recover its anti-MUC1 antibody responses. Cortisol, like other glucocorticoids, is known to induce apoptosis of mammalian T and B cells[38, 39] and inhibit cytokine production of other leukocytes[40]. Stress paradigms with animals suggest that endocrine factors released during stress modulate leukocyte trafficking and result in the redistribution of leukocytes between the blood and other immune compartments[41]. Such reductions in function and redistribution would be expected to significantly effect the ability of the immune system to respond to potential or ongoing immune challenges.

Considering the interactions between differential levels of cortisol and the immune response found here, the observed differential anti-MUC1 antibody response between the Intervention and Assessment only arms at 8 and 12 months would be predicted. Specifically, the presence of high levels of cortisol during the chemotherapy period (primarily from the initial to the 4 month assessment) for the Assessment only patients would be expected to contribute to greater damage to T and B cells, and the continued presence of cortisol post chemotherapy would slow down cell recovery. Higher levels of cortisol in the period immediately after chemotherapy would have a profound, long term effects, even if cortisol levels eventually return to normal. This continuing negative effect would be predicted to occur because there is a narrow window after chemotherapy during which antigen (MUC1) is present in circulation and could elicit antibody responses. If during that time, the intervention results in a reduction in cortisol, T and B cell recovery will coincide with that window. In contrast, if cortisol lowers slowly (or only minimally), T and B will not encounter their specific antigen and no antibody will be produced (In fact, mean cortisol levels for the Assessment only group remained at the initial baseline level or even increased further, rather than decline).

The major anti-MUC1 antibody response found in breast cancer patients is IgM. Production of IgM antibody is a result of a direct B cell activation on tandemly repeated epitopes along the MUC1 polypeptide core and is considered to be relatively helper T cell independent[28]. In addition, some IgG responses have been identified that depend on the activation of helper T cells specific for MUC1[42]. Reduction of anti-MUC1 antibody levels during and post chemotherapy in both groups of patients is a consequence of a direct lytic effect of chemotherapy on activated T and B cells. As noted above, the recovery of anti-MUC1 antibody responses in patients in the Intervention arm can be attributed to activation of memory B and T cells that have survived chemotherapy, and/or priming of newly emerging T and B cells on the circulating MUC1 antigen, expected to be present in the serum post tumor destruction[43,44]. These two events would be expected to contribute unequally in Stage II and Stage III patients and likely account for their differential anti MUC1 antibody responses (see Figure 3). Specifically, the memory cells are expected to be more responsible for recovering and maintaining anti-MUC1 antibody in Stage II patients. The tumor burden in these patients is smaller, and post surgery and chemotherapy there should be low amounts of MUC1 antigen present in circulation. These amounts may be sufficient to activate memory B cells that require very little antigen, but not to prime additional naïve B cells that require a much higher antigen dose. In Stage III patients, however, higher levels of MUC1 would be expected to be present due to more advanced disease, the activation of memory cells, and, in turn, the new naïve B cells can be recruited into the response. Such circumstances can account for the stronger recovery of antibody responses in Stage III patients.

There were several advantages of using anti MUC1 antibody as the immune outcome of this intervention. First, quantitative measures or even other functional assessments (e.g. NK cell lysis, T or B cell blastogenesis) provide a transient assessment of the stress environment rather than an adaptive (i.e. memory) response of the immune system. Importantly, T cell recognition of antigen through the T-cell receptor is the basis of a range of immunological phenomena, including T-cell helper and suppressor activity, cytotoxicity, and, possibly, NK cell activity. Second, the MUC1 response is specifically relevant to breast cancer, and moreover, the strength of the response is related to clinical outcomes (i.e., the disease free interval and overall survival[24]). Third, with the disease specificity of the MUC1 response, it serves as a plausible marker of an overall anti-tumor response in the patient.

Studies have shown improved survival for cancer patients following psychological interventions[45,46], though the mechanism(s) for these effects are unclear. Whether or not the immune responses shown here will have parallel clinical import remains to be determined, although the 12 month recurrence/survival data are in the hypothesized direction. Specifically, by the 12-month assessment, eight subjects had dropped from the study (3 Intervention, 5 Assessment only), five subjects had recurred or recurred and died from their disease (1 Intervention, 4 Assessment only), and 2 subjects had died of other causes (1 Intervention, 1 Assessment only). The convergence of psychologic, endocrine, and immune effects shown here provides an important empirical foundation for clarifying the biobehavioral mechanisms in the examination of the relationship between stress and cancer outcomes.

METHODS

Patient eligibility and data collection

Participants were 115 women who had been diagnosed and surgically treated for Stage II (84%) or III (16%) invasive breast cancer. At the time of accrual, women were from 14 to 101 days (M = 37 days, SD = 17) post surgery and had not yet begun their standard adjuvant therapy. The majority of participants (78%) were being treated at a NCI designated, University affiliated Comprehensive Cancer Center and the remainder (22%) were receiving treatment at local community hospitals.

Sociodemographic description of the sample revealed the following characteristics: racial distribution (88% Caucasian, 10% African American, 2% Hispanic); age (M = 51 years, SD =11; range 31 to 84 years); marital status (65% married, 26% divorced/widowed, 9% never married); education level (M = 15 years); employment status (65% employed full or part time; 35% unemployed outside the home or retired); and, annual personal income (M = $28,000, range of $2-$110,000).

Recruited consecutively from mid 1994 to early 1997, all women came to the General Clinical Research Center at the university or the outpatient breast cancer center for the collection of psychological, behavioral, and medical data, and a 60ml blood draw. Assessments were conducted between 8:00 am and 12:00 pm to reduce diurnal variability. After the initial assessment, patients were randomized between Intervention and assessment (n = 57) vs. Assessment only (n = 58) arms. Randomization was stratified by prognostic (i.e. tumor size/number of lymph nodes, estrogen receptor status, menopausal status) and psychosocial (i.e., presence/absence of a significant other) variables. All patients began their standard adjuvant cancer therapy following accrual and initial assessment, and were then reassessed at 4, 8, and 12 months. From the time of the initial to the 4 month assessment, 85% of the entire sample received chemotherapy. From the time of the 4 to the 8 month assessment, 22% of the entire sample received chemotherapy, and between the 8 and 12 month assessment 4% of the sample received chemotherapy.

Intervention protocol

The intervention was conducted in an outpatient psychological clinic in the Department of Psychology on the university campus. A biobehavioral model[27] provided the conceptual framework for the intervention. Six components, each with specific intervention strategies, were included: 1) stress reduction (i.e. training in progressive muscle relaxation, conceptualization for the relationship between stress and health); 2) enhancing quality of life (i.e. identifying sources of social support and improving support from friends and family; assertive communication; coping with body changes and enhancing sexuality; problem solving for cancer-related difficulties, e.g. fatigue); 3) increasing positive health behaviors (i.e. beginning/maintaining moderate exercise; breast cancer-relevant dietary/nutrition changes, e.g. increased fiber and lower fat intake); 4) decreasing negative health behaviors (i.e. reduce smoking, alcohol consumption); 5) improving compliance (e.g. seeking additional information about cancer treatments; assertive communication with health care providers); and, 6) support offered/received by therapists and group members.

The intervention was delivered in a group format, consisting of a cohort of 8-12 women and 2 Ph.D. clinical psychologists as therapists (B.A. and D. G.-K.). A single intervention cycle was 26 1.5 hour sessions (18 weekly + 8 monthly sessions) for a total of 39 therapy hours delivered over a 12 month period; six cohorts of patients completed the intervention. Reliability of the treatment procedures was insured by having the therapists follow a session-by-session written manual, provision of a modified therapy manual to the patients, and weekly meetings of the therapist team to review the previous session, rate the topic coverage, and prepare for the next session. Treatment "dose" to the women was documented; in session attendance was documented. Session absences were followed within 3 days by a telephone call to the woman from one of the therapists to provide coverage of the group session, including discussing the content of the week's intervention session, assigning the intervention 'homework,' and updating the patient on the concerns of the other group members.

Assessment only patients came to the Clinical Research Center (CRC) at the University

Hospital or the outpatient breast cancer center for the assessment interviews and blood draw. Women were reimbursed for parking ($4) and paid a modest fee ($20) for their time and effort for each assessment. Identical assessment procedures were followed for the patients randomized to the intervention arm.

Measures and Assays

Psychological: depressive symptoms. We employed the short form (IOWA version[47]) of the Center for Epidemiological Studies Depression Scale (CES-D)[48, 49]. This is a standardized self-report questionnaire used to identify current symptoms of depression, with an emphasis on depressed affect. The CES-D short form consists of 11 items (e.g. "I felt everything I did was an effort," "I feel sad") rated on a 3 point Likert scale from 'hardly ever or never" to "much or most of the time." Women responded based on their feelings during the previous week. Total scores can range from 0 to 22 with higher scores reflecting greater symptoms. Unlike other measures of depressive symptoms, the CES-D is relatively unaffected by physical symptoms and is, therefore, commonly used in research with medical patients[50]. Internal consistency reliability was .74.

Endocrine: Plasma cortisol. Cortisol was measured using chemiluminescence technology (Nichols Institute, San Juan Capistrano, CA.). The sensitivity of the assay (0.8 ug/dl) was adequate to measure cortisol in each sample. Large cortisol assays (usually 2 cohorts of 20 Ss each with all four assessments) were run to eliminate interassay variation. The inter and intra assay coefficient variations of the assay are less than 8%.

Immune: MUC1-specific antibodies. Venous blood was collected in 10 ml green top (heparin) tubes and mixed to avoid clotting. Tubes were then centrifuged at 1700 rpm for 10 minutes in Beckman GS-6R Centrifuge. With sterile technique, 5 ml of plasma was then removed, placing 1 ml into each of three cryovials and 2 ml. into one cryovial. Tubes were frozen at -20^{o} C and then subsequently moved for storage at -70^{o} C.

Microtiter plates (Immulon 4, Dynatech Labs) were coated with synthetic MUC1 peptide, 40 amino acids in length, corresponding to two tandem repeats from the MUC1 polypeptide core [(PDTRPAPGSTAPPAHGVTSA) x 2]. Each well was coated with 1ug of peptide dissolved in phosphate buffered saline (PBS). Following an overnight incubation at 40° C, the plates were washed twice with PBS and to each well was added 100 ul of a 2.5% solution of bovine serum albumin (BSA, Sigma Chemical Co., St. Louis, MO) in PBS to block uncoated plastic surfaces in the wells. This blocking step was performed for 1 hour at 22° C. The plates were then inverted to remove the blocking reagent (BSA-PBS). Various dilutions of patients' plasma samples were made in the blocking reagent (2.5% BSA-PBS) and 50 ul were added into the wells. Each dilution was tested in triplicate wells. An exact replica microtiter plate was prepared at the same time which was only "mock" coated with PBS without MUC1 peptide, blocked with BSA-PBS, and reacted with serial dilutions of the plasma samples. This plate served as a control for nonspecific binding.

Incubation of the peptide-coated and the control plates was for 1 hour after which the plates were washed 5 times with PBS containing 0.01% Tween 20 detergent. Each well then received 50ul of the secondary antibody, alkaline phosphatase conjugated goat anti-human Ig (anti IgG, IgM and IgA) (Sigma, #A3313), diluted 1:1000 in BSA-PBS. Following a 1 hour incubation, the plates were again washed 5 times with PBS-0.01% Tween. Each well then received 100ul of phosphatase substrate (Sigma #3104), at the concentration of 3ug/ml, diluted in 0.5mM $MgCl_2$, 0.05M Na_2CO_3. The reaction was terminated after 1 hour by adding 50ul of 0.05 M NaOH, and absorbency was measured at 492nm. The OD values from the wells on the control plate that did not receive MUC1 peptide were subtracted from the values in test wells containing peptide to determine antibody specific reactivity. These procedures were followed after the collection of the last serum samples; all time points for all subjects were run in the same assay. The assays were run multiple times.

Data analyses

Data were evaluated by intention to treat. We predicted that the psychological/behavioral intervention would yield positive psychological, endocrine, and immune effects for patients randomized to the intervention arm, in contrast to the effects for the patients randomized to the assessment only arm. We expected these responses to be manifest across time, with both groups having equivalent responses at the initial (pretreatment) assessment, with group differences emerging across the 4-, 8- and/or 12 month assessments. The period from the initial to the 4 month assessment was potentially the most stressful as it coincided with the delivery of 4 to 8 cycles of adjuvant chemotherapy for the majority (85%) of the patients in the study. As the intervention was intensive during the first 4 months (i.e. weekly intervention sessions), we anticipated the greatest reductions in stress (i.e. cortisol) and improvements in psychological responses (i.e. depressive symptoms) during the difficult, initial to 4 month period. We anticipated some lessening of stress reduction or psychological improvements as the patients in the intervention arm shifted from the weekly to the monthly intervention sessions during the 4 to 12 month follow ups, as maintenance of psychological/behavioral effects is difficult to achieve[51]. We predicted a replication of the general effects of the intervention across stage, but we anticipated that intervention effects might be strongest for women with stage III disease, as effectiveness of psychological interventions is robust for individuals with more extensive disease[12].

For all measures--psychological, endocrine, and immune--a repeated measures analysis of variance (ANOVA) model was used. The primary hypothesis was tested by examining the interaction between Group x Time, with Group (Intervention vs. Assessment only) and Stage (II vs. III) as between subjects factors and Time (initial, 4-, 8-, and 12 months) as a within (repeated measures) factor. Finally, as the mucin assay was conducted across three target: cell ratios, 1:20, 1:40, and 1:80, we ran an ANOVA model for each, with the expectation that significant interactions should, in general, be replicated across the cell ratios. The latter strategy can demonstrate the reliability of an intervention effect on the antibody response.

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Table 1 Analysis of Variance Interaction Results For MUC1 Across Three Dilutions

Within subjects

F	df	1:20	1:40	1:80
Group x Time	3	4.30*	3.56*	2.61 [a]
Group x Time x Stage	3	3.72*	3.67*	3.01[a]
Within-group error	231	(.260)	(.047)	(.028)

Note: Values enclosed in parentheses represent mean square errors.

* $p < .05$

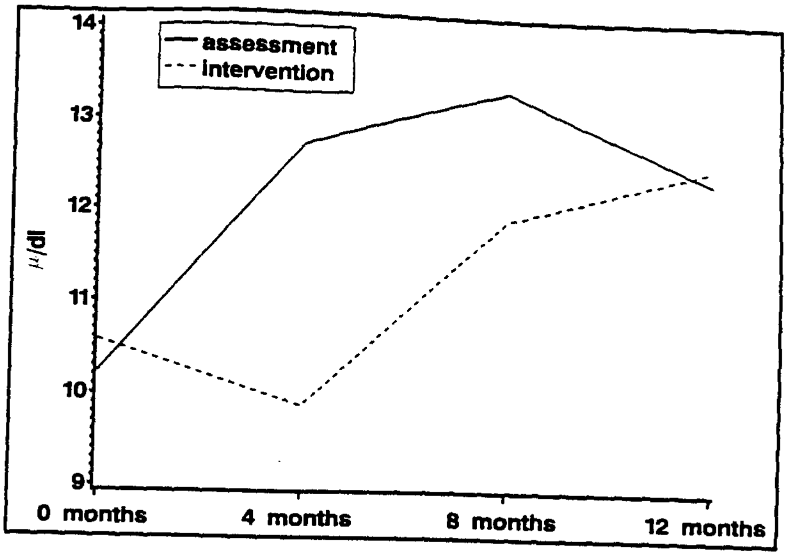
[a] $p < .10$

Figure Captions

Figure 1. Mean cortisol levels for the Intervention and Assessment only study arms across Time for initial (0), 4-, 8-, and 12-month assessments. The figure illustrates the Group x Time interaction, indicating significant group differences over time. Specifically, cortisol levels for patients in the Intervention arm showed a significantly greater decrease from 0 to 4 months than cortisol levels for patients in the Assessment-only arm.

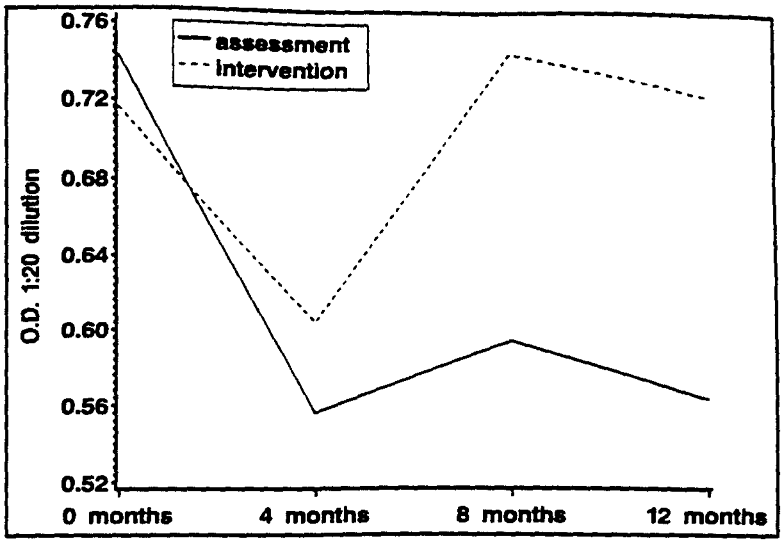
Figure 2. Mean anti-MUC-1 antibody levels for 1:20 (top, a), 1:40 (middle, b), and 1:80 (bottom, c) dilutions for Intervention and Assessment only study arms across Time for initial (0), 4-, 8-, and 12-month assessments. Figures illustrate Group x Time interactions at 1:20 ($p < .05$), 1:40 ($p < .05$), and 1:80 ($p < .10$). Specifically, anti-MUC-1 antibody levels for patients in the Intervention arm showed a significantly greater increase in their anti-MUC1 antibody response from 0 to 8 months and 0 to 12 months than did patients in the Assessment only arm.

Figure 3. Mean anti-MUC-1 antibody levels for the 1:20 dilution for Intervention and Assessment only study arms across Time for initial (0), 4-, 8-, and 12- month assessments for patients with Stage II (top) versus Stage III (bottom) disease. Figures illustrate Group x Time x Stage interaction ($p < .05$). Specifically, the 1:40 dilution shows a significantly larger increase in anti-MUC-1 antibody response levels from 0 to 12 months for the Intervention arm patients than for the Assessment-only arm patients. This effect (see Fig. 2 above) can be seen most clearly at this dilution with the Stage III patients.

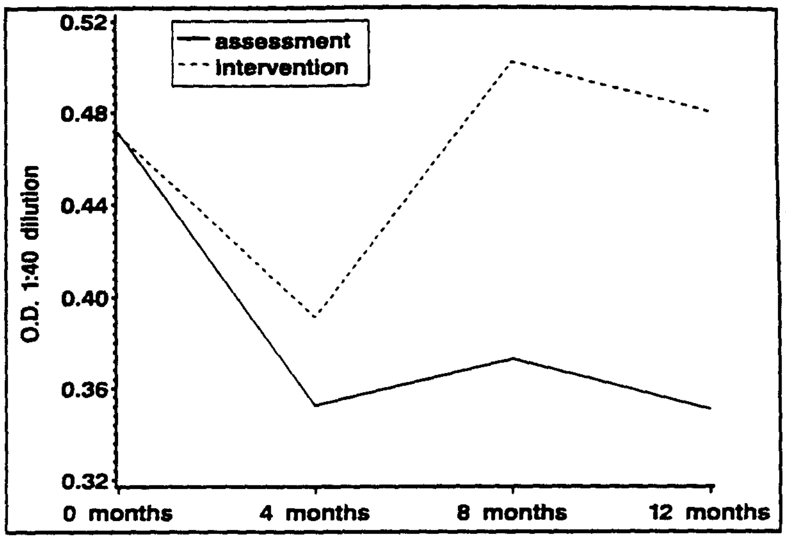


assessment
intervention
14
13
12
11
10
9
μ/dl
0 months
4 months
8 months
12 months

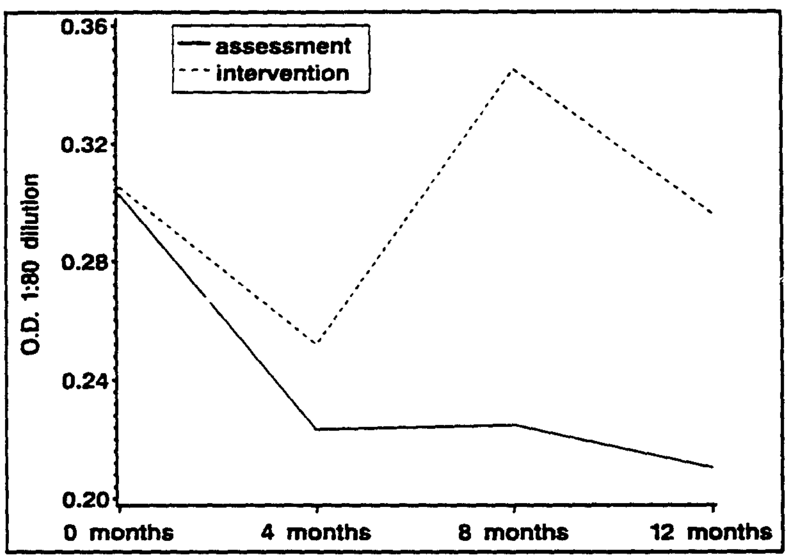
a.


assessment
intervention
O.D. 1:20 dilution
0.76
0.72
0.68
0.64
0.60
0.56
0.52
0 months
4 months
8 months
12 months

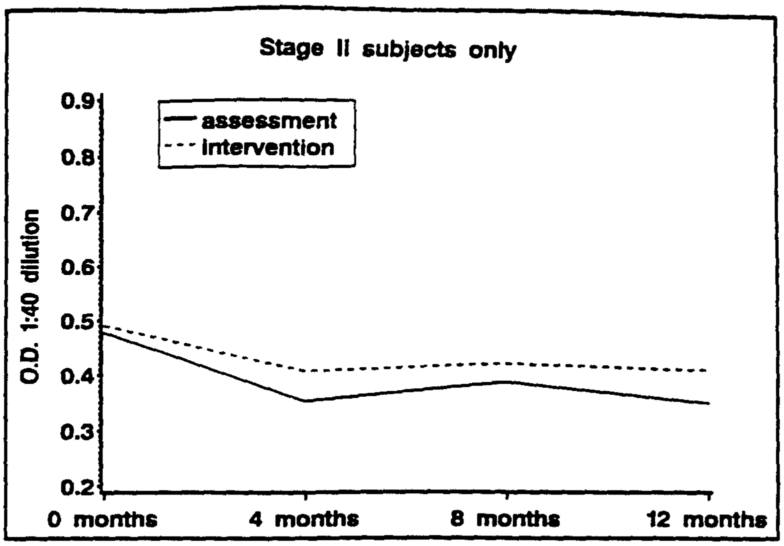
b.


assessment
intervention
O.D. 1:40 dilution
0.52
0.48
0.44
0.40
0.36
0.32
0 months
4 months
8 months
12 months

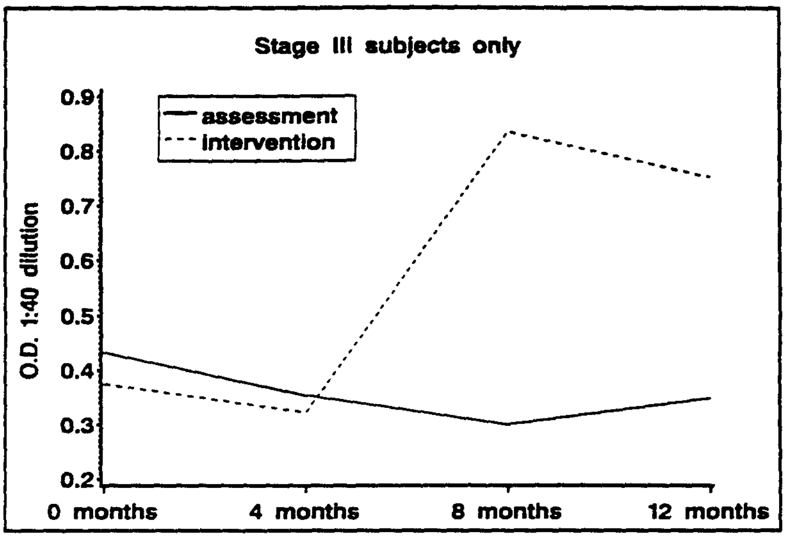
c.


assessment
intervention
O.D. 1:80 dilution
0.36
0.32
0.28
0.24
0.20
0 months
4 months
8 months
12 months

a.


Stage II subjects only
assessment
intervention
O.D. 1:40 dilution
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0 months
4 months
8 months
12 months

b.


Stage III subjects only
assessment
intervention
O.D. 1:40 dilution
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0 months
4 months
8 months
12 months

Women Succeeding in Science in 1999: A Multidisciplinary Poster Session - March 3, 1999

ABSTRACT

Conducting Clinical Research with Breast Cancer Patients: Issues of Recruitment and Retention

Deanna M. Golden-Kreutz, PhD, William Farrar, M.D., and Barbara L. Andersen, PhD

We are testing a biobehavioral model of cancer stress and disease course (Andersen, Kiecolt-Glaser, & Glaser, 1994) which includes psychological (stress and quality of life), behavioral (health behaviors and compliance), and biological (immune) data with a 5 year randomized clinical trial. Women with stage II or III breast cancer are randomized between psychological/behavioral intervention (lasting 1 year) and assessment only arms. Issues of recruitment and retention are vital if a trial such as this is to successfully answer empirical questions (e.g., are intervention groups associated with longer survival?). We currently have a refusal rate of 31.8% and a drop out rate of 6.6% at a mean participation of 16 months (range = 1-30; initial data with n = 137). We have identified reasons for refusal and termination of participation (e.g, stress, distance, etc.) and discuss various strategies (e.g., addressing obstacles to participation) that researchers may use in recruiting and retaining cancer patients in intensive randomized longitudinal clinical trials.

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World Congress of Behavioral and Cognitive Therapies

Acapulco, Mexico, July 21-26, 1998

BENEFITS OF COGNITIVE/BEHAVIORAL INTERVENTIONS FOR WOMEN WITH BREAST CANCER.

Authors: Golden-Kreutz, D., DiLillo, V., Farrar, W., & Andersen, B.

We are testing a biobehavioral model of cancer stress and disease course (Andersen, Kiecolt-Glaser, & Glaser, 1994) which includes psychological (stress and QoL), behavioral (health behaviors and compliance), and biologic (immune and endocrine) factors as well as health outcomes (disease free interval) with a 5 year randomized clinical trial. Women with stage II or III breast cancer are randomized into either an intervention or a no intervention (assessment only) arm. The intervention consists of two phases, an intensive phase of weekly meetings for four months and a subsequent maintenance phase of monthly meetings for an additional eight months. Intervention components include disease/treatment information, progressive muscle relaxation training, social support identification/usage, assertive communication skills training, body image and sexuality issues, and improving health behaviors (treatment compliance, diet, exercise). Data are obtained every 4 months during the first year and every 6 months over the next 4 years. It is expected that women being treated with the intervention will show lowered stress, increased QoL, more positive health behaviors/fewer negative ones, greater compliance, and fewer negative changes in immune and endocrine functioning, over time. To date, we have collected initial data on 160 women. Data on the impact of the cognitive/behavioral intervention will be presented. Implications for future research in this area will be discussed.

STRESS REDUCTION AND ENHANCED COPING FROM A PSYCHOLOGICAL/BEHAVIORAL INTERVENTION FOR WOMEN WITH REGIONAL BREAST CANCER: STUDIES FROM THE STRESS AND IMMUNITY BREAST CANCER PROJECT

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Background: The adjustment process for breast cancer survivors may be burdensome and lengthy. There is also ample evidence from the psychoneuroimmunology (PNI) literature showing that adults undergoing acute and/or long term stressors experience high rates of adjustment difficulties and important biologic effects--persistent down regulation of the immune system. Thus, deteriorations in quality of life (QoL) with cancer are underscored if they also have adverse health effects. To guide the research, a biobehavioral model of cancer stress and disease course was proposed (Andersen, Kiecolt-Glaser, & Glaser, 1994). This model includes psychological (stress and quality of life), behavioral (health behaviors and compliance), and biologic (immune) factors, and specifies the pathways by which health outcomes (e.g. disease endpoints--recurrence, disease free interval) might be affected. We are testing portions of the model with an experiment--a randomized clinical trial of a psychological intervention. *Purpose:* Data from this project will provide 1) a test of a psychological intervention which is designed to reduce stress, enhance quality of life, increase positive health behaviors, decrease negative health behaviors, and improve compliance; 2) a test of the immune enhancing effects of such interventions; 3) a test of the health (cancer outcome) consequences of such interventions; and, 4) a test of immunity as one mechanism which may link psychological/behavioral variables to cancer. *Method:* Women with stage II or III breast cancer are randomized between psychological/behavioral intervention and no intervention arms. Our hypothesis is that women being treated with the psychological intervention protocol will show lowered stress, increased QoL, more positive health behaviors and fewer negative ones, greater compliance, and an increase in immune functioning. *Results:* Preliminary analyses of 100 of the 200 subjects to be accrued show that the psychological intervention results in significant reductions in stress, enhanced coping, and improvements in health behaviors.*Conclusions:* The data show that the psychologic effects of structured interventions are significant. Moreover, these gains are maintained at follow up. *Implications:* Further studies will need to determine if immune and/or health consequences emerge for those individuals reporting high levels of stress reduction, and also clarify the mechanisms for such positive effects.

Key Words: Breast Cancer, Stress, Behavioral, Psychological

The work was supported by the U.S. Army Research and Materiel Command under DAMD17-94-J-4165 and DAMD17-96-1-6294.

Presentation

ABSTRACTS

The Gerontological Society of America
50th Annual Scientific Meeting
November 14-18, 1997
Cincinnati, Ohio

OLDER ADULTS IN LONGITUDINAL CLINICAL TRIALS: ISSUES OF RECRUITMENT AND RETENTION.

D.M. Golden-Kreutz, & B.L. Andersen
Department of Psychology, The Ohio State University, Columbus, Ohio 43210-1222.

We are testing a biobehavioral model of cancer stress and disease course (Andersen, Kiecolt-Glaser, & Glaser, 1994), collecting psychological (stress and quality of life), behavioral (health behaviors and treatment compliance), and biological (immune and endocrine) data on women diagnosed with stage II or III breast cancer. Participants are randomized into a psychosocial intervention (lasting 1 year) or an assessment only arm. Participation includes 12 assess -ments over a 5 year period. Our sample (n=126) ranges in age from 31-84 (m=52). Approximately 30% of the sample are 60+ years of age. The majority of subjects who have refused participatrion or have dropped out after initial participation are women between the ages of 35-55. Our current total refusal rate is 25% and the drop out rate is 10%. When women over 60 years of age refuse participation or drop out they do so primarily because of distance/driving concerns while younger women tend to refuse/drop out due to time constraints and children in the home. In order to include and maintain the participation of older adults in longitudinal clincial trials, issues specific to this age group must be addressed. We have found that older adults are interested in participating in longitudinal clinical trials. We discuss various means that researchers may use in helping older adults achieve the above.

Presentation

RECRUITMENT AND RETENTION: CONDUCTING CLINICAL RESEARCH WITH BREAST CANCER PATIENTS

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Poster presented at the Annual Meeting of the American Psychological Association (August, 1997), Chicago, Illinois

ABSTRACT

We are testing a biobehavioral model of cancer stress and disease course (Andersen, Kiecolt-Glaser, & Glaser, 1994) which includes psychological (stress and quality of life), behavioral (health behaviors and compliance), and ɔiologic (immune) data with a 5 year randomized clinical trial. Women with stage II or III breast cancer are ·andomized between psychological/behavioral intervention (lasting 1 year) and assessment only arms. Issues of ·ecruitment and retention are vital if a trial such as this is to successfully answer empirical questions (e.g., are ntervention groups associated with longer survival?). We currently have a refusal rate of 31.8% and a drop out rate ›f 6.6% at a m = 16 months (range = 1-30) of participation (initial data with n = 137). We have identified reasons for efusal and termination of participation (e.g., stress, distance, etc) and discuss various strategies (e.g., addressing ›bstacles to participation) that researchers may use in recruiting and retaining cancer patients in intensive randomized ›ngitudinal clinical trials.

Appendix C
- Unpublished Data -
In progress

RUNNING HEAD: MEASUREMENT INVARIANCE OF THE PSS

Examining Measurement Invariance in Longitudinal Clinical Research:

A Test of the PSS in Women with Breast Cancer

Deanna M. Golden-Kreutz, Georita M. Frierson,

Michael W. Browne, and Barbara L. Andersen

Key words: Perceived Stress Scale, CEFA, measurement invariance

Abstract

Examining Measurement Invariance in Longitudinal Clinical Research:

A Test of the PSS in Women with Breast Cancer

The use of measures which demonstrate measurement invariance (for example, the stability of factor loadings or regression slopes over time; Byrne, Shavelson, & Methen, 1989) in longitudinal clinical research is important for the accurate interpretation of results, especially if the results have implications regarding the success and/or selection of psychological interventions (Pentz & Chou, 1994). Unfortunately, in examining the underlying or latent factors of measures, researchers have long made critical errors in their selection of statistical strategies. For instance, one "package" of choices which can lead to incorrect interpretations of data and the poor "recovery" of underlying factors is principal component analyses with varimax rotation (a procedure more appropriate for data reduction) and using the greater than 1 eigenvalue rule to identify factors (see Fabrigar, Wegener, MacCallum, & Strahan, in press, for a review). More appropriate choices for identifying underlying factors and their invariance is exploratory or confirmatory factor analysis (EFA and CFA, respectively), although it has been argued that CFA has advantages over EFA in assessing invariance (see Long, 1983; Marsh & Hocevar, 1985 for reviews). However, in CFA some factor loadings are constrained to be zero and if one of the zero constraints is inappropriate not only will the overall fit of the model be affected but the inappropriate zero loading is not easily detected. Comprehensive Exploratory Factor Analysis (CEFA; Browne, Cudeck, Tateneni, & Mels, 1998), a computer program for carrying out exploratory factor analysis, allows rotation to a partially specified target (Browne, 1972), therefore failure of a rotated loading to be reasonably close to a specified zero value is more easily identified as an inappropriate specification. Besides the ability to carry out target rotations, CEFA also provides confidence intervals for the rotated factor loadings. Neither of these facilities is currently available in other factor analytic programs, making the use of CEFA an attractive alternative.

The purpose of our study was in exploring the factor solution and stability of the factor loadings over time (measurement invariance) of the Perceived Stress Scale, a measure of globally perceived stress (PSS; Cohen, Kamarck, & Mermelstein, 1983) using the CEFA program. We tested the PSS in a cancer population because, while it is well documented that cancer diagnosis and treatment are distressing (e.g., Andersen, 1992; Andersen, Anderson, & deProsse, 1989; Weisman & Worden, 1976) and that, over time, the distress remits (Edgar, Rosberger, & Nowlis, 1992; Lee et al., 1992), studies examining the invariance of measures used to assess distress (e.g., stress, depressive and/or anxiety symptoms) over time have not been conducted. Therefore, we explored the measurement invariance of the PSS in a sample of women prospectively followed during their treatment for breast cancer, one of the most commonly diagnosed cancers in the United States (Landis, Murray, Bolden, & Wingo, 1999). In particular, we were interested in seeing if the previous factor solution of the PSS (2 factors: 1) perceived coping and 2) perceived distress as determined by principal component analysis with varimax rotation; Cohen & Williamson, 1986; Hewitt, Flett, & Mosher, 1992; Martin, Kazarian, & Breiter, 1995), would be revealed and if this solution remains stable over time in a stressed sample when more rigorously investigated with the newly available CEFA program.

Method

Sample and Procedure

Women recently diagnosed and undergoing treatment for regional breast cancer were studied every four months for one year (i.e., initial, 4, 8, and 12 month assessment time points). See Table 1 for sociodemographic and cancer-specific disease characteristics of the sample at the initial assessment time point. Participants in the current study were accrued from mid-1994 to mid-1999 for a larger prospective, longitudinal study (The Stress and Immunity Breast Cancer Project; see Andersen, Kiecolt-Glaser, & Glaser, 1994 for a review). At the time of the initial assessment, all participants had been surgically treated (lumpectomy or mastectomy) within the preceding 3 months but had not yet begun adjuvant treatment (e.g., chemotherapy, radiation). The majority of women were in active treatment during their 4 and 8 month assessments and finished by the 12 month assessment, approximately one year post-diagnosis. Psychological, behavioral, and medical/treatment information were collected through an interview and questionnaires at the University's General Clinical Research Center or the breast cancer clinic. Disease and surgery information were verified using information from the women's medical charts/reports and confirmed with primary care providers. All women were paid $20.00 for their participation.

Measure

The PSS, a measure of globally perceived stress, is a standardized self-report questionnaire used to determine the extent to which a person judges her/his life to be unpredictable, uncontrollable, and overloading (Cohen et al., 1983). Based on Cohen and Williamson's (1986) recommendation, the ten item PSS-10 was used for its improved psychometric properties (e.g., internal reliability) over other versions of the PSS. The two factors previously identified, perceived coping and perceived distress consist of 4 and 6 items, respectively (Cohen & Williamson, 1983; Hewitt et al., 1992; Martin et al., 1995). Examples of the questions include: "How often have you felt nervous or stressed" and "How often have you felt confident about your ability to handle your personal problems." Women rated how often they experienced these feelings in the past month on a 5-point Likert scale (from never=1 to very often=5). Four of the items are reversed score to control for social desirability. Total scores range from 0 to 40 and higher scores indicate greater overall stress. Coefficient alpha reliability ranges from .75 to .86 in the literature (Cohen & Williamson, 1986; Hewitt et al., 1992; Martin et al., 1995; & Pbert, Doerfler, & DeCosimo, 1992).

Factor Analytic Strategy

The solution and stability of the factor matrix was investigated using maximum likelihood factor analysis at each of the assessment time points. Because factors are correlated to some degree, oblique rotation to a partially specified target (Browne, 1972) was carried out in order to obtain a clearer factor solution. Loadings anticipated to be zero were minimized in the rotation process and values of the remaining loadings were left unspecified. Thus a pattern suggested by current research (2 factors: perceived coping and perceived distress) was tested and a rotation to a solution as close to the target as possible was carried out. As an additional check, we also conducted factor analyses for 1 (underfactored) and 3 (overfactored) factor solutions. The extent to which the target was appropriate is judged by verifying 1) whether rotated loadings corresponding to zero target elements are small, and 2) whether rotated loadings corresponding to unspecified target elements are large. Confidence intervals are obtained on all loadings after rotation as a guide to judgement when investigating the magnitude of the factor loadings. This was repeated for each measurement time point of the PSS-10.

Results and Discussion

Factor Analyses

The Root Mean Square Error of Approximation (RMSEA; Steiger & Lind, 1980; Browne & Cudeck, 1992), measuring goodness of fit, for the factor solutions at all 4 assessment time points ranged from .094 to .165 for one factor, from .064 to .101 for two factors and from .028 to .069 for three factors (see Table 2 for all RMSEA scores). The RMSEA values for the one-factor solution were unsatisfactory. Furthermore, the residual matrix for the one-factor solution showed a pattern of large residuals suggesting that further factors are necessary. The RMSEA values were satisfactory on the whole for the two and three-factor solutions. The three-factor solution at each of the four time points showed evidence of overfactoring. For instance, in the oblique (direct quartamin) rotation there was only one high loading on the third factor at each time point and the position of this high loading changed from one time point to another. However, the two-factor solution demonstrated stability over all four time points with consistent high loadings that corresponded to the unspecified target elements and reflected previous findings (Cohen et al., 1983; Hewitt et al., 1992; Martin et al., 1995). Furthermore, the loadings corresponding to zero target elements were small with associated confidence intervals not generally overlapping zero. The residuals for the two-factor solution at all four time points appeared satisfactory since they did not demonstrate a pattern among the items. Thus, we retained the two-factor solution as revealing the most appropriate factor solution of the PSS-10 and found this solution to be stable over time. Due to space limitations, Table 3 contains the factor loadings and confidence intervals across all four assessment time points for the two-factor solution only.

Descriptives of the PSS-10 in a Breast Cancer Sample

Internal consistency, means, standard deviations, and sample sizes across the four assessment time points are shown in Table 4. Reliability coefficients, using Cronbach's alpha, ranged from .78 to .89 and are consistent with previous research demonstrating internal consistency of the PSS-10 (Cohen & Williamson, 1986; Hewitt et al., 1992; Martin et al., 1995; & Pbert et al., 1992). While the means of the total scale at the 4, 8, and 12 month time points are consistent with those found in a sample of community dwelling adults (13.02; Cohen & Williamson, 1986) the overall mean at the initial time point is approximately 1 SD higher. This suggests that at the initial assessment women may have been more stressed. To test if stress decreased significantly over time, as found in other studies of women with breast cancer (e.g., Edgar et al., 1992; Lee et al., 1992), we conducted a repeated measures ANOVA to compare the means across time. These analyses indicted a significant decrease in stress, $F(3, 112) = 14.19$, $p < .0001$. Furthermore, as expected pairwise comparisons indicated that mean differences were only significant when comparing the initial time point with the latter time points (p's $< .05$).

Conclusions

We recommend the use of CEFA when conducting exploratory factor analytic studies of measurement invariance in longitudinal clinical research. The CEFA program has several distinct advantages over other currently available computer programs including: 1) the ability to carry out target rotations which increases the likelihood of correctly identifying an inappropriate specification and 2) computing confidence intervals for the rotated factor loadings which allows for greater precision in identifying the true population value. Specifically, the CEFA program revealed, consistent with previous principal component analyses, that the PSS-10 is composed of two factors, perceived coping and perceived distress. More importantly, the PSS-10 demonstrates measurement invariance in a clinical population, women recently diagnosed and being treated for breast cancer. Thus, one can be confident about decisions made about the impact of a psychological intervention when using this measure in a cancer population.

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Table 1.

Sociodemographic and Disease Characteristics of Sample

Sociodemographics	**N (%)**
Age (years)	M(SD) = 51(11)
Race:	
White	171(90)
Minority	21(10)
African -American	19(9)
Latino	2(1)
Living with spouse/partner:	
Yes	139(72)
No	53(28)
Education (years):	
<12 years	7(3.6)
12 years	46(24)
13-15 years	52(27.1)
16 years	34(17.7)
>16 years	50(27)
Annual family income:	
<$15,000	15(7)
$15-29,000	29(15)
$30-49,000	43(22)

$50-79,000	42(22)
≥$80,000	19(28)
Disease Characteristics	
Stage:	
II	129(86)
III	26(14)
Surgery Type:	
Lumpectomy	76(39)
Mastectomy	101(61)
Modified Radical	95(57)
Radical	1(1)
Elective Bilateral	5(3)

Note. N = 192. Disease staging was based on the American Joint Committee on Cancer and the International Union Against Cancer staging systems.

Table 2.

Estimated RMSEA values for 1-, 2-, 3- factors

	Initial	**4- month**	**8-month**	**12- month**
1 Factor	.165	.094	.133	.117
2 Factor	.068	.063	.101	.064
3 Factor	.062	.028	.069	.037

Note: Rough guidelines estimates for RMSEA values: <.05= indicates close fit ; .05-.08 = indicates reasonable fit, .08-.10= indicates mediocre fit, and > .10 indicates unacceptable fit.

Table 3. Factor Loadings and Confidence Intervals of PSS Items

Scale Items	**Initial Assessment (n = 192)**		**4 Month Assessment (n = 144)**		**8 Month Assessment (n = 139)**		**12 Month Assessment (n = 123)**	
	Factor 1 Coping L(CI)	**Factor 2 Distress L(CI)**	**Factor 1 Coping L(CI)**	**Factor 2 Distress L(CI)**	**Factor 1 Coping L(CI)**	**Factor 2 Distress L(CI)**	**Factor 1 Coping L(CI)**	**Factor 2 Distress L(CI)**
1. How often have you been angered because of things that happened that were outside of your control?	-.01 (-.12; .10)	.64 (.53; .75)	-.09 (-.27; .10)	.61 (.42; .80)	-.30 (-.41; -.11)	.84 (.69, 1.00)	.03 (-.14; .22)	.63 (.45; .80)
2. How often have you felt difficulties piling up so high that you could not over come them?	.04 (-.07; .15)	.70 (.60; .79)	.12 (-.07; .28)	.70 (.54; .85)	.08 (-.06; .23)	.67 (.53; .80)	.13 (-.03; .29)	.70 (.55; .85)
3. How often have you felt you were unable to control the important things in your life?	.09 (-.01; .20)	.70 (.60; .79)	-.18 (-.37; .01)	.94 (.76; 1.12)	.09 (-.05; .23)	.67 (.53; .80)	-.25 (-.43; -.08)	1.00 (.83; 1.20)
4. How often have you felt nervous or "stressed"?	.66 (.55; .77)	-.10 (-.20; .00)	.75 (.57; .94)	-.11 (-.28; .06)	.41 (.25; .57)	.15 (-.01; .31)	.65 (.47; .83)	-.14 (-.29; .01)
5. How often have you felt that you could not cope with all the things that you had to do?	.72 (.62; .81)	.08 (-.02; .18)	.40 (.22; .59)	.39 (.21; .56)	.53 (.39; .67)	.21 (.07; .36)	.79 (.63; .96)	.02 (-.16; .19)
6. How often have you been upset because of something that happened unexpectedly?	-.01 (-.12; .10)	.71 (.62; .81)	.20 (-.02; .41)	.35 (.140; .56)	.50 (.35; .66)	.20 (.05; .36)	.09 (-.10; .28)	.55 (.37; .74)
7. How often have you been able to control irritations in your life?	.60 (.49; .71)	.03 (-.08; .14)	.70 (.51; .88)	-.05 (-.22; .12)	.30 (.13; .46)	.39 (.23; .55)	.57 (.40; .75)	.19 (.02; .37)
8. How often have you felt that you were on top of things?	.85 (.75; .94)	.06 (-.04; .16)	.68 (.49; .84)	.22 (.05; .40)	.83 (.70; .95)	.05 (-.08; .19)	.72 (.56; .87)	.19 (.03; .36)

9. How often have you felt confident about your ability to handle your personal problems?	.13 (-.24; -.03)	.78 (.68; .88)	.18 (-.01; .36)	.54 (.36; .71)	.05 (-.09; .19)	.70 (.57; .84)	.05 (-.13; .22)	.66 (.50; .83)
10. How often have you felt that things were going your way?	.06 (-.04; .17)	.69 (.59; .79)	.09 (-.09; .26)	.70 (.55; .87)	.65 (.52; .78)	.23 (.10; .36)	.10 (-.07; .26)	.68 (.53; .84)
Average CI Width	.17	.20	.37	.35	.23	.29	.27	.35

Table 2.

Means, Standard Deviations, Sample Size, and Coefficient Alpha Reliability for Sample

Assessment	Total Score	Perceived Coping	Perceived Distress
Initial			
M(SD)	18.65(6.88)	6.51(3.15)	12.15(4.82)
N	192	192	192
Alpha	.86	.81	.86
4 Month			
M(SD)	14.80(6.92)	5.11(3.04)	9.74(4.44)
N	141	141	141
Alpha	.89	.80	.84
8 Month			
M(SD)	14.79(6.78)	4.99(3.02)	9.80(4.37)
N	139	139	139
Alpha	.88	.78	.83
12 Month			
M(SD)	14.50(6.93	4.87(2.91)	9.63(4.66)
N	123	123	123
Alpha	.89	.82	.86

DEPARTMENT OF THE ARMY
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Rec'd 7/24/2001

REPLY TO
ATTENTION OF:

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SUBJECT: Request Change in Distribution Statement

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2. Point of contact for this request is Ms. Judy Pawlus at DSN 343-7322 or by e-mail at judy.pawlus@det.amedd.army.mil.

FOR THE COMMANDER:

PHYLLIS M. RINEHART
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Information Management

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